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Short Reports

Trends in the Diagnosis and Treatment of Chronic Hepatitis B in Karachi, Pakistan

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Abstract

Aims: *Aim of this study was to analyze diagnostic and therapeutic trends of physicians regarding Chronic Hepatitis B (CHB) in Karachi since Pakistan is endemic area for viral hepatitis B.*

Methods: *A questionnaire was distributed to about 100 physicians / doctors in different hospitals of Karachi. The questionnaire assessed diagnostic trends, prescribing habits for Chronic Hepatitis B (CHB) treatment and patients monitoring and follow ups by the physician.*

Results: *About 100 doctors from Karachi participated in the study (response rate: 72%). 34.72% doctors had experience of treating less than 10 patients per month. Majority of the doctors (79.16%) used HBsAg (anti-HBsAg seroconversion), (61.11%) used liver function tests (LFTs) and hepatitis B virus (HBV) DNA levels were used by doctors (47.22%) as diagnostic parameters for CHB. HBV-DNA levels were the most commonly used parameter to confirm diagnosis and was used by 86.11 % doctors. Treatment of CHB was started upon various indications i.e. 58.33% doctors used HBV DNA level when it is e"20,000 IU/mL (10^5 copies/mL) ; 36.11% used HBV DNA when it is e" 2000 IU/mL (10^4 copies/mL) and 29.16% doctors used Serum alanine aminotransferase (ALT) when it was elevated for 3-6 months. Most of the doctors (38.88%) had experience with Interferon alfa and Pegylated IFN-a 2a, (26.38%) with Lamivudine and (25%) with Entecavir. For treatment, 41.66% of doctors recommended Pegylated IFN-a 2a for HBeAg positive CHB patients whereas 22.22% of doctors treated HBeAg negative CHB Patients with Entecavir. HBV DNA levels and alanine aminotransferase (ALT) levels were most commonly used to monitor therapy by 73.61% and 52.77% doctors respectively. Frequency of follow-up was after 3 months by most of the doctors (63.88%). According to 23.61% doctors, 5 to 10% of patients required add- on treatment or switching from the previous regimen. According to most doctors (68.05%), polymerase chain reaction (PCR) - negativity was an important indication of improved response and outcome to anti-viral therapy.*

Conclusion: *CHB management decision varies from physician's perspective and is not always based on scientific decision. Mostly doctors used HBV DNA level as indication for treatment when it is e" 2000 IU/mL (10^4 copies/mL) and prescribed Interferon alfa and Pegylated IFN-a 2a to their patients. Monitoring of therapy was usually done by observing HBV DNA levels and alanine aminotransferase (ALT) levels of patients and frequency of follow-up was after 3 months by most of the doctors. Add- on treatment or switching is also required by some patients and improved response to treatment was assessed by PCR negativity. Management of CHB can be improved through CME (continual medical education) and practical training.*

Keywords: *Hepatitis, Viral hepatitis, Chronic Hepatitis B, Interferon Alpha, Lamivudine.*

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Introduction

Hepatitis B is a worldwide healthcare problem, especially in developing areas. An estimated one third of the global population has been infected with the hepatitis B virus (HBV). Approximately 350 million people are lifelong carriers, and only 2% spontaneously seroconvert annually. Ongoing vaccination programs appear to be promising in the attempt to decrease the prevalence of HBV disease. Antiviral treatment may be effective in approximately one third of the patients who receive it, and for selected candidates, liver transplantation currently seems to be the only viable treatment for the latest stages of hepatitis B. The hepatitis B virus (HBV) is transmitted hematogenously and sexually. The outcome of this infection is a complicated viral-host

interaction that results in either an acute symptomatic disease or an asymptomatic disease. Patients may become immune to HBV, or they may develop a chronic carrier state. Later consequences are cirrhosis and the development of hepatocellular carcinoma (HCC).[1-4]

The prevalence of hepatitis B (HBsAg) reported was 2.5% in Pakistan. Overall HBeAg positivity was 14.4% with 17% in Balochistan, 15.3% in Sindh, 14.1% in Punjab and 8.4% in NWFP. For HBV only, the prevalence within provinces showed 2.5% in Sindh, 2.4% in Punjab, 1.3% in NWFP and 4.3% in Balochistan.[5] Pakistan is more aggressive to this disease due to co-infection and super-infection with delta virus. The case fatality rate with delta infection is 30.2 % in Sindh and Punjab. Intra-familial spread of hepatitis B is quite high and the highest reported in spouses is 23.5%. Pakistan has a high carrier rate of hepatitis B. It is between 10 to 14 % with enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA) techniques. Hepatitis B (HB) is more prevalent in males as compared to females (8.13% and 6.7% respectively). In patients with chronic and fulminant type of hepatitis, 52 % of the cases had delta infection. The incidence of delta infection was 14 % in patients who had hepatitis B during dialysis. More than 17.6 % of the random blood donors were found positive for anti-HBs. In a number of studies, the prevalence of anti-HBs was 12.2 - 40 percent.[6]

Persistently elevated serum HBV DNA and alanine amino-transferase (ALT) levels have been found to be the most important predictors of future complications in CHB patients, including cirrhosis, hepatic decompensation, HCC, and death [7-14]. The decision to treat CHB with antivirals is primarily based upon the results of two laboratory tests: high levels of serum HBV DNA, indicative of active viral replication, and elevated serum ALT levels, indicative of ongoing liver injury.[15,16] While the ALT level is an important criterion for assessing the requirement for therapy in most treatment guide- lines,[17-19] it can be affected by non-HBV-related factors (e.g., body mass index, gender, exercise, abnormal lipid and carbo-hydrate metabolism, and co-morbidities) .[20,21] Therefore, ALT results should not be used as the sole criterion for initiating treatment and should instead be assessed in conjunction with HBV DNA levels.[20] Hyperglobulinemia is another finding, predominantly with an elevation of the IgG globulins. Mildly elevated levels of rheumatoid factor (RF) are usually present.[22,23]

Treatment of chronic hepatitis B (CHB) has improved in recent years with introduction of new oral antiviral drugs.[24] Evidence suggests that effective antiviral treatment could slow the progression of CHB.[25] Chronic Hepatitis B is being treated by Gastroenterologists and Internists in Pakistan. The main goal of CHB therapy is to prevent the progression of liver disease.[26] Currently approved drugs for the treatment of CHB include interferons (interferon-a2b and peginterferon-a2a) and oral nucleoside or nucleotide analogs (lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate).[17, 15] Although ongoing trials are investigating new types of medications, such as tenofovirdisoproxil in combination with emtricitabine, clevudine (l-FMAU), and therapeutic vaccines, it appears that lamivudine and telbivudine are not recommended as first-line agents in the treatment of hepatitis B disease.[27]

Optimal management of CHB requires routine monitor-ing, even when patients are asymptomatic, in order to determine the extent of liver disease progression and the timing of treatment initiation. Two major CHB treatment guidelines are widely used in the US: AASLD (American Association for the Study of Liver Diseases) guidelines and the US Treatment Algorithm.[17,20] The AASLD guidelines currently recommend both serum ALT and serum HBV DNA monitoring in untreated CHB patients, with treatment initiated in those with HBV DNA levels of at least 20,000 IU/ ml and ALT more than twice the upper limit of normal. There are likely to be multiple barriers to appropriate initiation of treatment; one major factor may be that physi-cians are not appropriately monitoring the laboratory values necessary to determine the correct point for treatment initiation. AASLD guidelines recommend monitoring of both HBV DNA and ALT levels at least annually,[17] however, a study suggests that adherence falls below recommendations.[28] In contrast, the US Treatment Algorithm currently recommends laboratory mon-itoring every 3-6 months.[20]

Material and Methods

The intent of this study is to examine the quality of care receive by CHB patients by assessing diagnostic and therapeutic trends of physicians regarding Chronic Hepatitis B in Karachi. The study also aimed to identify predictors of laboratory monitoring and to identify predictors of subse-quent initiation of antiviral treatment (oral nucleoside/ nucleotide analogs, or interferon/peg interferon).

A questionnaire was developed for the purpose of survey and is divided into four different sections: the first section includes questions related to the diagnosis of Chronic Hepatitis B and indications for treatment; the second section is designed to investigate about the treatment of Chronic Hepatitis B and drugs preferred in CHB patients; the third section focuses on monitoring and follow up of CHB patients; and the last section is about socioeconomic class of patients and frequency of contact of doctors to CHB patient and their treatment.

In Karachi, about 100 physicians / doctors were randomly selected and the questionnaire was distributed among them by researchers from February to May, 2012. The study is non interventional and it does not involve patients and hence no ethical approval was needed. Data collection was followed by statistical analysis.

Results and Discussions

The response rate by the doctors who participated in the study was 72% which included Physicians, Postgraduates, Residents and House Officers. 34.72% of doctors had experience of treating less than 10 patients per month and 26.38% of doctors treated greater than 20 patients per month. Socioeconomic class of majority of patients was poor (88.88%).

Diagnosis of Chronic Hepatitis B

Majority of the doctors used HbsAg (79.16%), liver function tests (LFTs) (61.11%) and (HBV) DNA levels (47.22%) as diagnostic parameters for CHB. Other serological markers/ histological/ laboratory findings used for diagnosis of CHB by the doctors were HBeAg (38.88%), Liver biopsy (36.11%), abdominal ultrasonography (31.94%), CBC (22.22%) and HBcAb (22.22%) as indicated in table 1. HBV-DNA levels were the most commonly used parameter to confirm diagnosis and was used by 86.11 % doctors. Other parameters used by the doctors include serum ALT levels (29.16%) and extent of liver damage (29.16%) as indicated in table 2. Treatment of CHB was started upon various indications i.e. 58.33% doctors used HBV DNA level when it is e"20,000 IU/mL (10^5 copies/mL); 36.11% doctors used HBV DNA when it is e" 2000 IU/mL (10^4 copies/mL) and 29.16% used Serum alanine aminotransferase (ALT) levels elevated for 3-6 months as indicator for treatment. For the HBeAg-positive patient population identified with evidence of chronic HBV disease, treatment is advised to be initiated when the HBV DNA level is e"20,000 IU/mL (10^5 copies/mL) and when serum alanine aminotransferase (ALT) is elevated for 3-6 months. For the HBeAg-negative chronic population with hepatitis B disease, treatment can be initiated when the HBV DNA is e" 2000 IU/mL (10^4 copies/mL) and serum ALT is elevated for 3-6 months. Albumin and PT / INR are also used for diagnosis of the disease by some physicians. According to some physicians when HBV DNA (Qualitative) confirms the diagnosis of Chronic Hepatitis B, then there is need for assessment of HBV DNA levels (Quantitative).

Table-I

Table Shows Serological Markers/ Histological/ Laboratory Findings / Used For Diagnosis of CHB by Doctors In Karachi

Laboratory findings	Percentages
Liver function tests (LFTs)	61.11%
CBC	22.22%
(HBV) DNA levels	47.22%
HBsAg	79.17%
HBeAg	38.89%
HBcAb	22.22%
Abdominal ultrasonography	31.94%
Liver biopsy	36.11%
HDVAb	8.33%

Table II

Table shows parameters used to confirm diagnosis

Parameters	Percentages
Age of infection	5.56%
Mode of transmission	9.72%
Serum ALT levels	29.17%
Immune status	9.72%
Genotype	12.50%
Status of infection: HBV-DNA levels	86.11%
Extent of liver damage	29.17%

Table-III

Shows serological markers/ histological/ laboratory findings / used for monitoring of CHB

Laboratory Findings	Percentages
HBV DNA levels	73.61%
Alanine aminotransferase (ALT) levels	52.78%
Antigen-antibody HBV profile	18.06%
Liver biopsy	11.11%
Alpha-fetoprotein (AFP) measurements	9.72%
Abdominal ultrasonography	11.11%

Treatment of Chronic Hepatitis B

Most of the doctors (38.88%) had experience with Interferon alfa and Pegylated IFN-a 2a, 26.38% doctors with Lamivudine and 25% doctors with Entecavir. For HBeAg positive patients, 41.66% of doctors recommended Pegylated IFN-a 2a, 29.16% advised Interferon alfa, 18.05% advised Entecavir, 16.66% recommended Lamivudine and 13.88% advised Tenofovir. 22.22% doctors treated HBeAg negative CHB patients with Entecavir, 20.83% doctors treated with Lamivudine and 20.83% doctors treated with Pegylated IFN-a 2a as shown in Fig.-1. Patients were treated for 6 months and 1 Year by 50% and 26.38% doctors, respectively. Duration

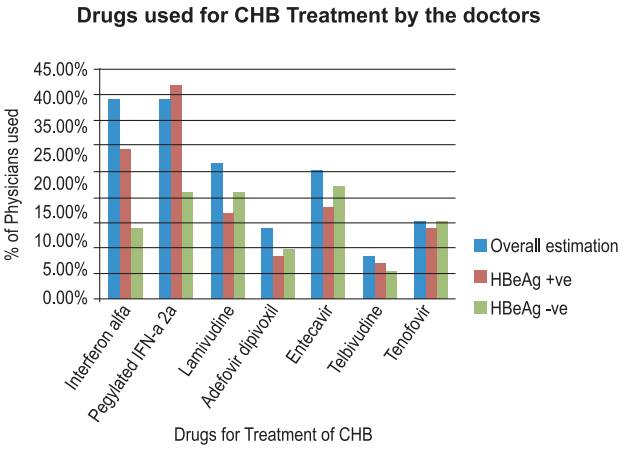

Fig.-1: *Shows drugs used for chb treatment by the doctors*

of treatment varies from patient to patient i.e. for those who have already developed CLD, treatment continues lifelong; for HbeAg-positive patients treatment is continued till HbeAg sero-conversion plus 6 months and for HbeAg-negative patients, it is continued till Hbs -Ag sero-conversion plus 6 months. Furthermore, three HBV DNA negative patients continued for 6 months apart.

Monitoring & Follow-up

HBV DNA levels and alanine aminotransferase (ALT) levels were most commonly used to monitor therapy by 73.61% and 52.77% doctors, respectively; only 18.05% doctors used antigen-antibody HBV profile as indicated in table 3. Frequency of follow-up was after 3 months by most of the doctors (63.88%), and only 19.44% followed-up after 6 months. 5 to 10% of patients required add- on treatment or switching according to 23.61% of doctors. The important indications of improved response and outcome to anti-viral therapy were PCR negativity, HbeAg seroconversion and ALT Normalization as reported by (68.05%), (45.83%) and (29.16%) doctors respectively.

Blood CP, Creatinine, HbeAg, HbsAg and Anti Hbe (antigen-antibody HBV profile) are also used for monitoring by some physicians. Patients who are potential for treatment cessation or switching are Non-Responders according to 58.33% of doctors. HbsAg sero conversion is also reported as an important indication of improved response and outcome to anti-viral therapy.

Conflict of Interest : None

References

1. Fattovich G, Giustina G, Schalm SW, et al. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The Eurohep Study Group on Hepatitis B Virus and Cirrhosis. Hepatology 1995; 21(1):77-82
2. Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 1997; 336(26):1855-9
3. Yu MC, Yuan JM, Ross RK, et al. Presence of antibodies to the hepatitis B surface antigen is associated with an excess risk for hepatocellular carcinoma among non-Asians in Los Angeles County, California. Hepatology 1997; 25(1):226-8
4. Yang HI, Yeh SH, Chen PJ, et al. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. J Natl Cancer Inst 2008; 100(16):1134-43
5. Prevalence of Hepatitis B & C in Pakistan - Pakistan Medical Research Council (PMRC) http://www.pmrc.org.pk/part-1.pdf
6. K Khalida, situation of hepatitis in Pakistan and preparation of diagnostic reagents for the detection of HBsAG (ELISA) - Pakistan Research Repository. 1997, pg: 186 http://www.pmrc.org.pk/hepatitisbc.htm
7. Sorrell MF, Belongia EA, Costa J, et at. National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. Ann Intern. Med 2009; 150: 104-10
8. Wolters Kluwer Pharma Solutions, Inc. Chronic Hepatitis B, Total Prescription Sales Data, 2009- 2010. Philadelphia, PA, March 2010.
9. Chen CJ, Yang HI, Su J. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006; 295:65-73.
10. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006; 130:678-86
11. Iloeje UH, Yang HI, Jen CL. Risk and predictors of mortality associated with chronic hepatitis B infection. Clin Gastroenterol Hepatol 2007; 5:921-31
12. Chen G, Lin W, Shen F, et al. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. Am J Gastroenterol 2006; 101:1797- 803
13. Liu CJ, Chen BF, Chen PJ. Role of hepatitis B viral load and basal core promoter mutation in hepatocellular carcinoma in hepatitis B carriers. J Infect Dis 2006; 193:1258-65
14. Ohata K, Hamasaki K, Toriyama K, et al. High viral load is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis B virus infection. J Gastroenterol Hepatol 2004; 19:670-5
15. Gish RG. Hepatitis B treatment: Current best practices, avoiding resistance. Cleve. Clin J Med 2009; 76 Suppl 3: S14-9