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AN OBSERVATIONAL STUDY ON CLINICAL SAFETY AND EFFICACY OF ANTIVIRAL MEDICATIONS USED IN CHRONIC HEPATITIS-B VIRUS INFECTION

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ABSTRACT

Hepatitis B is serious liver illness that is brought on by hepatitis B virus. It is classified into two types- acute and chronic hepatitis. Antivirals are the best choice of treatment for Hepatitis-B. Tenofovir (25mg and 300mg) and Entecavir (0.5mg) are currently used medications to control viral replication and suppress viral DNA levels. The study was a single centered, observational study that included 60 chronic hepatitis-B patients. They were split into two groups of patients prescribed with Tenofovir and Entecavir. Our study was conducted on 60 patients out of which 81.66% were found to be males and 18.33% were found to be females. Among them, most of the patients belonged to the age group 41-60 years (51.66%). In 51 patients taking Tenofovir monotherapy, 41 patients (80.40%) were having ≤2000 IU/mL. In 6 patients taking Entecavir monotherapy, 3 patients (50%) were having ≤2000 IU/mL. In 3 patients taking Dual therapy, 2 patients (66.67%) were having ≤2000 IU/mL. Among 60 patients, ADRs were reported in 41 patients (68.33%). Commonly reported ADRs were weakness, headache, dizziness, abdominal pain. These are mild and occasional. 73.40% patients reported ADRs while using Tenofovir and 83.33% patients reported ADRs while using Entecavir.

From our study, it was observed that Tenofovir is having good safety and efficacy (80.40%) whereas Entecavir is having 50% efficacy. Tenofovir safety and efficacy is much more when compared to safety and efficacy of Entecavir.

Keywords: Liver, Hepatitis, Tenofovir, Entecavir.

1. INTRODUCTION

Chronic Hepatitis B virus (HBV) infection remains a significant global health problem. Despite the availability of HBV vaccines for three decades, the global prevalence of chronic HBV infection has only declined slightly, from 4.2% in 1990 to 3.7% in 2005 [1]. Worldwide, however, the absolute number of persons chronically infected has increased from 223 million in 1990 to 240 million in 2005. In the United States, based on 1999-2006 data from the National Health and Nutrition Examination Survey, the prevalence of chronic HBV infection was estimated to be 0.27% [2]. However, the National Health and Nutrition Examination Survey under sampled high-prevalence groups, so when accounting for immigration from endemic countries, as many as 2.2 million US residents (instead of 730,000) may have chronic HBV infection [3].

The natural course of chronic HBV infection consists of four characteristic phases: immune tolerant, hepatitis B e antigen (HBeAg)-positive immune active, inactive, and HBeAg-negative immune active phases [4]. The immune tolerant phase is characterized by the presence of HBeAg, normal alanine aminotransferase (ALT) levels, and high levels of HBV DNA, usually well over 20,000 IU/mL. The immune active phases, also called HBeAg-positive or HBeAg-negative chronic hepatitis, are characterized by intermittently or persistently elevated ALT with active hepatic inflammation and HBV DNA generally above 2000 IU/mL. The inactive phase is characterized by absence of HBeAg and presence of hepatitis B e antibody, normal ALT in the absence of other concomitant liver diseases, and undetectable or low levels of HBV DNA, generally below 2000 IU/mL. Although not all patients go through each phase and immune responses to HBV during each phase have not been fully characterized, this classification schema provides a useful framework when developing a management approach for chronic HBV infection.

Antiviral drugs are a class of medicines particularly used for the treatment of viral infections. Specific antiviral drugs are used for treating specific viruses just like the antibiotics for bacteria. Antiviral drugs, unlike the most antibiotics, do not destroy their target pathogens; rather inhibit their development. As the viruses use the host's cells to replicate, hence makes it difficult to design a safe and effective antiviral drug. Therefore, it is difficult to find the drug targets that would interfere with the virus without damaging the host's cells. Furthermore, the major complications in developing anti-viral drugs and vaccines are because of viral variation [5]. One of the important ways of finding antiviral drugs is the computer based drug discovery and for this approach nelfinavir is an example discovered in the 1990s for the treatment of human immunodeficiency virus (HIV) infection [6].

In spite of modern tools and stringent measures for the quality control only a few antiviral drugs are getting approved for the use of human either due to the side effects or resistance to antiviral drugs. With increase in the awareness about the viruses, their mechanism of infection and the rapid evolvement of novel strategies and techniques for antiviral will speed up the novel antiviral drugs development [7]. The current scenario all over the world indicates that continuous emergence of microbial threats at an accelerating pace, mainly due to unprecedented climate change and globalisation [8].

Hepatitis B virus is still a significant problem for worldwide public health. If the person is infected with HBV, it is important to stop the replication of virus in Hepatitis patient. There are various antiviral medications used in Chronic HBV infection (Tenofovir, Entecavir, Lamivudine, Telbivudine).These antiviral medications vary in their efficiency and ADR profile. Thus, it is necessary to do research on the clinical efficacy and safety of different antiviral medications used in treatment of chronic hepatitis-B infection. The main goal of our study is to assess the clinical efficacy and safety of antiviral medications used in treatment of chronic hepatitis-B virus infection. The objectives of study were to assess the efficiency of antiviral drugs used to treat chronic HBV infection, to evaluate ADRs due to usage of antiviral drugs, to assess patient demographic details, family history, to assess viral load.

2. MATERIAL AND METHODS

2.1. Study design

An observational study on chronic hepatitis-B infection and its treatment.

2.2. Source of data collection

- Patient Data collection form.
- Patient case note or prescription (Outpatient, Inpatient).
- Laboratory test reports.
- Patient medication history.

2.3. Inclusion criteria

- All Age groups
- Patients with confirmed diagnosis of HBV infection.
- Patients on antiviral medications.
- Patients who are conscious, co-operative, and willing to provide Informed consent.

2.4. Exclusion criteria

- Patients who are unconscious, non-co-operative.
- Pregnant and Lactating women.

Sample size was 60 patients and study period was 6months at Gleneagles Global Hospitals.

3. RESULTS

3.1. Distribution of patients based on gender

Out of 60 patients, 49 (81.66%) were found to be male and 11 (18.33%) were found to be female.

Table 1: Gender wise distribution

Gender	Tota no. of patients	Percentage
Male	49	81.66%
Female	11	18.33%

3.2. Age wise distribution of patients

Total age was categorized at the interval of 10. Out of 60 patients, 9 patients (15%) were under the age group of 21-30, 9 patients (15%) were under the age group of 31-40, 16 patients (26.66%) were under the age group of 41-50, 15 patients (25%) were under the age group of 51-60, 7 patients (11.67%) were under the age group of 61-70, 4 patients (6.67%) were under the age group of 71-80.

Out of 49 male patients, 5 patients were under the age group of 21-30, 7 patients were under the age group of 31-40, 15 patients were under the age group of 41-50, 11 patients were under the age group of 51-60, 7 patients were under the age group of 61-70 and 4 patients were under the age group of 71-80.

Out of 11 female patients, 4 patients were under the age group of 21-30, 2 patients were under the age group of 31-40, 1patient was under the age group of 41-50, 4 patients were under the age group of 51-60.

Table 2: Age wise distribution

Age	Total no. of patients	Male	Female	Percentage
21-30	9	5	4	15%
31-40	9	7	2	15%
41-50	16	15	1	26.66%
51-60	15	11	4	25%
61-70	7	7	0	11.67%
71-80	4	4	0	6.67%

3.3. Weight wise distribution of patients

Out of 60 patients, 22 patients (36.67%) were found to be below or equal to 60 kgs and 38 patients (63.33%) were found to be above 60 kgs.

Table 3: Weight wise distribution of patients

Weight	Total number of patients	Percentage
Below or equal to 60kgs	22	36.67%
Above 60 kgs	38	63.33%

3.4. Distribution of patients based on co-morbidities

Out of 60patients, 37patients (61.67%) had co-morbidities and 23 patients (38.33%) had no co-morbidities.

Table 4: Distribution based on co-morbidities

Co-morbidities	Number of patients	Percentage
With co-morbidities	37	61.67%
Without co-morbidities	23	38.33%

3.5. Distribution of patients with comorbidities based on gender

Out of 37 patients with co-morbidities, 32 patients (86.49%) were found to be male, and 5 patients (13.51%) were found to be female.

Table 5: Distribution of patients with overall co-morbidities based on gender

Gender	Total no. of patients	Percentage
Male	32	86.49%
Female	5	13.51%

3.6. Distribution of patients with individual comorbidities based on gender

Out of 49 male patients, 17 patients had no co-morbidities, 7 patients were having diabetes mellitus, 4 patients were having hypertension, 3 patients were having both DM and HTN, 1 patient was having kidney disease, 17 patients were having other co-morbidities.

Out of 11 female patients, 6 patients had no co-morbidities, 1 patient was having diabetes mellitus, 2 patients were having hypothyroidism, 2 patients were having other co-morbidities.

Out of 60 patients, 23 patients (38.33%) had no co-morbidities, 8 patients (13.33%) were having diabetes mellitus, 4 patients (6.67%) were having hypertension, 3 patients (5%) were having both DM and HTN, 2 patients (3.33%) were having hypothyroidism, 1 patient (1.67%) was having kidney disease, 19 patients (31.67%) were having other co-morbidities.

Table 6: Distribution of co-morbidities based on gender

Co-morbidities	Male	Female	Percentage
Normal	17	6	38.33%
Diabetes mellitus	7	1	13.33%
Hypertension	4	0	6.67%
DM+HTN	3	0	5%
Hypothyroidism	0	2	3.33%
Kidney disease	1	0	1.67%
Others	17	2	31.67%
Total	49	11	100.00%

3.7. Distribution based on family history

Out of 60 patients, 4 patients (6.67%) were having family history of Hepatitis-B, 56 patients (93.33%) had no family history of Hepatitis-B.

Table 7: Distribution based on family history

Family history	No. of patients	Percentage
Yes	4	6.67%
No	56	93.33%

3.8. Distribution of patients based on marker detected

Out of 60 patients, HBsAg was detected in 41 patients (68.34%), anti-HBs was detected in 2 patients (3.33%), HBeAg was detected in 2 patients (3.33%), anti-HBe was detected in 8 patients (13.33%), 1 patient (1.67%) was found to have anti-HBe positive with HBeAg negative, 1 patient (1.67%) was found to have anti-HBe, anti-HBc positive with HBeAg negative, total anti-HBc was found to be positive in 5 patients (8.33%).

3.9. Distribution of patients based on symptoms

Out of 60 patients, symptoms were seen in 49 patients (81.67%) and 11 patients (18.33%) had no symptoms.

Table 8: Distribution of patients based on marker detected

Marker detected	Number of patients	Percentage
HBsAg	41	68.34%
Anti-HBs	2	3.33%
HBeAg	2	3.33%
Anti-HBe	8	13.33%
Anti-HBe with HBeAg negative	1	1.67%
Anti-HBe, anti-HBc with HBeAg negative	1	1.67%
Total anti-HBc	5	8.33%

Table 9: Distribution based on symptoms

Symptoms	Number of patients	Percenatge
With Symptoms	49	81.67%
Without Symptoms	11	18.33%

3.10. Distribution of patients based on ascites and PHT-esophageal varices

Out of 60 patients, 13 patients (21.67%) had ascites, 6 patients (10%) had PHT with esophageal varices and11 patients (18.33%) had both ascites and PHT with esophageal varices and 30 patients (50%) had no symptoms of ascites and PHT with esophageal varices.

Table 10: Distribution of patients based on ascites and PHT-esophageal varices

Symptoms	Number of patients	Percentage
Ascites	13	21.67%
PHT-esophageal varices	6	10%
Ascites and PHT-esophageal varices	11	18.33%
Without ascites and PHT-esophageal varices	30	50%

3.11. Distribution of patients with PHT-esophageal varices based on weight

Out of 17 patients having PHT with esophageal varices, 8 patients (47.06%) are less than 60 kgs and 9 patients (52.94%) are more than 60 kgs.

3.12. Distribution of patients based on cirrhosis

Out of 60 patients, 23 patients (38.33%) were having cirrhosis and 37 patients (61.67%) were not having cirrhosis.

Table 11: Distribution of patients with PHT-esophageal varices based on weight

Weight	Number of patients with PHT-esophageal varices	percentage
Below or =60kgs	8	47.06%
Above 60 kgs	9	52.94%

Table 12: Distribution based on cirrhosis

Cirrhosis	Number of patients	Percentage
With Cirrhosis	23	38.33%
Without Cirrhosis	37	61.67%

3.13. Distribution of patients based on type of cirrhosis

Out of 23 patients with cirrhosis, 17 patients (73.91%) were having decompensated cirrhosis, 6 patients (26.09%) were having compensated cirrhosis.

Table 13: Distribution based on type of cirrhosis

Type of cirrhosis	Number of patients	Percentage
Decompensated cirrhosis	17	73.91%
Compensated cirrhosis	6	26.09%

3.14. Distribution of patients based on presence of HCC

Out of 60 patients, HCC is seen in14 patients (23.33%) and HCC is not seen in 46 patients (76.67%).

Table 14: Distribution based on presence of HCC

HCC	Number of patients	Percentage
With HCC	14	23.33%
Without HCC	46	76.67%

3.15. Distribution of patients based on child-turcotte-pugh score

Out of 60 patients, 21 patients (35%) were CTP-A, 27 patients (45%) were CTP-B, and 12 patients (20%) were CTP-C. Child A-least severe, 95% chances of survival rate (1-5years), Child B-moderately severe, 75% chances of survival rate (1-5years) Child C-most severe, 50% chances of survival rate(1-5years).

3.16. Distribution of patients based on prothrombin time

Out of 60 patients, 41 patients (68.33%) had prothrombin time within the normal range and 19 patients (31.67%) had increased prothrombin time.

Table 15: Distribution of patients based on CTP score

CTP score	Number of patients	Percentage
A	21	35%
B	27	45%
C	12	20%

Table 16: Distribution of patients based on prothrombin time

Prothrombin time	Number of patients	Percentage
Normal	41	68.33%
Increased	19	31.67%

3.17. Distribution of patients based on albumin

Out of 60 patients, 36 patients (60%) had albumin within the normal range and 24 patients (40%) had decreased albumin level.

Table 17: Distribution of patients based on albumin

Albumin	Number of patients	Percentage
Normal	36	60%
Decreased	24	40%

3.18. Distribution of patients based on drug using

Out of 60 patients, 42 patients (70%) were taking Tenofovir alafenamide, 9 patients (15%) were using Tenofovir disoproxil fumarate, 6 patients (10%) were using Entecavir, 2 patients (3.33%) were using both Entecavir and TAF,1patient(1.67%)was using both Entecavir and TDF.

Table 18: Distribution based on drug using

Drug	No. of patients	Percentage
Tenofovir alafenamide (TAF)	42	70%
Tenofovir disoproxil fumarate (TDF)	9	15%
Entecavir	6	10%
Entecavir and TAF	2	3.33%
Entecavir and TDF	1	1.67%

3.19. Efficacy of tenofovir

Out of 51 patients taking Tenofovir, 41 patients (80.40%) have HBV DNA load ≤2000 IU/mL, 4 patients (7.84%) have HBV DNA load between 2000-5000 IU/mL and 6 patients (11.76%) have HBV DNA load>5000 IU/mL.

Table 19: Efficacy of Tenofovir

Viral DNA load	Number of patients	Percentage
≤2000IU/mL	41	80.40%
2000-5000IU/mL	4	7.84%
>5000IU/mL	6	11.76%

3.20. Efficacy of entecavir

Out of 6 patients taking Entecavir, 3 patients (50%) have HBV DNA load ≤2000 IU/mL, 0 patients have HBV DNA load between 2000-5000IU/mL and 3 patients (50%) have HBV DNA load>5000IU/mL.

Table 20: Efficacy of Entecavir

Viral DNA load	Number of patients	Percentage
≤2000IU/mL	3	50%
2000-5000IU/mL	0	0
>5000IU/mL	3	50%

3.21. Efficacy of dual therapy

Out of 3 patients taking Dual therapy (Tenofovir and Entecavir), 2 patients (66.67%) have HBV DNA load ≤2000IU/mL, 0 patient has HBV DNA load between 2000-5000IU/mL and 1 patient (33.33%) has HBV DNA load>5000IU/mL.

Table 21: Efficacy of Dual therapy

Viral DNA load	Number of patients	Percentage
≤2000IU/mL	2	66.67%
2000-5000IU/mL	0	0
>5000IU/mL	1	33.33%

3.22. Distribution of patients based on ADRs

Out of 60 patients, 41patients (68.33%) experienced ADRs and 19patients (31.67%) had no ADRs.

Table 22: Distribution of patients based on ADRs

ADRs	Number of patients	Percentage
With ADRs	41	68.33%
Without ADRs	19	31.67%

3.23. Distribution of patients based on ADRs induced by drugs

Out of 41 patients taking Tenofovir alafenamide, 29 patients (69.04%) were having ADRs, out of 9 patients taking Tenofovir disoproxil fumarate, 7 patients (77.77%) were having ADRs and out of 6 patients taking Entecavir, 5 patients (83.33%) were having ADRs.

Table 23: Distribution of patients based on ADRs induced by drugs.

Drug inducing	Number of patients	Percentage
Tenofovir alafenamide	29	69.04%
Tenofovir disoproxilfumarate	7	77.77%
Entecavir	5	83.33%

3.24. Distribution of patients based on ADRs induced by tenofovir alafenamide

Out of 42 patients taking Tenofovir alafenamide, 9 patients (21.43%) experienced weakness, 8 patients (19.04%) experienced headache, 6 patients (14.3%) experienced abdominal pain, 4 patients (9.52%) experienced fatigue, 2 patients (4.76%) experienced nausea and 13 patients (30.95%) had no ADRs.

Table 24: Distribution of patients based on ADRs induced by Tenofovir alafenamide

ADRs	Number of patients experienced	Percentage
Weakness	9	21.43%
Headache	8	19.04%
Abdominal pain	6	14.3%
Fatigue	4	9.52%
Nausea	2	4.76%
Nil	13	30.95%

3.25. Distribution of patients based on ADRs induced by tenofovir disoproxil fumarate

Out of 9 patients taking Tenofovir disoproxil fumarate, 2 patients (22.22%) experienced insomnia, 2 patients (22.22%) experienced headache, 3 patients (33.34%) experienced weakness and 2 patients (22.22%) had no ADRs.

3.26. Distribution of patients based on ADRs induced by entecavir

Out of 6 patients taking Entecavir, 2 patients (33.33%) experienced headache, 1 patient (16.67%) experienced fatigue, 2patients (33.33%) experienced dizziness and 1 patient (16.67%) had no ADR.

Table 25: Distribution of patients based on ADRs induced by Tenofovir disoproxil fumarate.

ADRs	Number of patients experienced	Percentage
Insomnia	2	22.22%
Headache	2	22.22%
Weakness	3	33.34%
Nil	2	22.22%

Table 26: Distribution of patients based on ADRs induced by Entecavir.

ADRs	Number of patients experienced	Percentage
Headache	2	33.33%
Fatigue	1	16.67%
Dizziness	2	33.33%
Nil	1	16.67%

4. DISCUSSION

We have conducted an observational study to evaluate the clinical safety and effectiveness of antiviral medications used in treatment of chronic hepatitis-B infection. The study was carried out over a six-month period in 60 individuals with chronic hepatitis-B infection based on inclusion and exclusion criteria. Oral nucleoside analogue antiviral drugs were administered to the patients (Tenofovir, entecavir).

For chronic hepatitis-B infection, men were more likely than women to be infected. In a sample of 60 patients, 49 (81.67%) were found to be male and 11 (18.33%) to be female.

Patients age was categorized into 6 classes-21-30, 31-40, 41-50, 51-60, 61-70, 71-80. Highest number of patients that are 51.66% are under the age group of 41 - 60. 22 patients (36.67%) among 60 patients were below or equal to 60kgs and 38 patients (63.33%) among 60 patients were above 60kgs.

Out of 60 patients, over 37 patients (61.67%) were having co-morbidities. Diabetes mellitus (13.33%) was mostly seen among patients with co-morbidities. 4 (6.67%) of the 60 patients had genetic predisposition to hepatitis-B infection.

Virologic marker HBsAg was detected in 68.34% patients with chronic hepatitis-B infection. Among the patients having HBsAg, 73.17% patients were found to

be male, and 26.82% patients were found to be female, and concludes that male patients had considerably greater HBsAg-positive rates than female patients.

Among 60 patients, 49 patients (81.67%) had symptoms like abdominal distension, pedal edema. Out of 60patients, ascites was seen in many patients that is in 13 patients (21.67%), PHT with esophageal varices was seen in 6 patients (10%) and 11 patients (18.33%) were having both ascites and PHT with esophageal varices. PHT with esophageal varices was seen more in patients (52.94%) above 60kgs.

Among the complications, 23 patients (38.33%) out of 60 patients had cirrhosis in which 17 patients (73.91%) were having decompensated cirrhosis and 6 patients (26.09%) were having compensated cirrhosis. HCC is seen in14 patients (23.33%) among 60patients.

CLD was staged based on Child-turcotte-pugh (CTP) score. 35% patients were grouped under 'A' score having 95% chances of survival rate for 1-5 years, 45% patients were grouped under 'B' score having 75% chances of survival rate for 1-5 years and 20% patients were grouped under 'C' score having 50% chances of survival rate for1-5years.

Majority of patients that is 51 patients (85%) out of 60 patients were taking Tenofovir, 6 patients (10%) were taking Entecavir, and 3 patients (5%) were taking dual therapy of Tenofovir and Entecavir.

Out of 51 patients using Tenofovir, 41 patients (80.40%) have ≤2000 IU/mL viral DNA. Among 6 patients using Entecavir, 3 patients (50%) have ≤2000 IU/mL viral DNA and over 2 patients (66.67%) out of 3 patients taking dual therapy have ≤2000IU/mL viral DNA.

ADRs were assessed and evaluated by using Naranjo causality ADR assessment scale. Out of 60 patients taking drugs, 41 patients (68.33%) were having ADRs, and 19 patients (31.67%) had no ADRs.

Among the study population of 60 patients, 29 patients (69.04%) were having ADRs among 42 patients receiving Tenofovir alafenamide.

Out of 9 patients using Tenofovir disoproxil fumarate, 7 patients (77.77%) were having ADRs. Among 6 patients taking Entecavir, 5 patients (83.33%) were having ADRs.

Efficacy of Tenofovir was 80.40%. Efficacy of Entecavir was 50%. Efficacy of dual therapy was 66.67%.These adverse drug reactions were minor and had no significant effect on the patient's quality of life.

5. CONCLUSION

We have conducted an observational study on the clinical safety and effectiveness of antiviral medications used in treatment of chronic hepatitis-B infection during a six-month period in a tertiary care institution. We used a sample size of 60. Among these male patients were 49 and female were11.

Between the ages of 41 and 60 made up the majority (51.66%) of the patients in them.

Patients were prescribed with antiviral medications in the treatment. They are Tenofovir and entecavir.

Tenofovir was prescribed to 51 patients. Entecavir was prescribed to 6 patients. Combination of entecavir and tenofovir was prescribed to 3patients. From our study the efficacy of these antivirals was evaluated by monitoring HBV DNA levels. In 51 patients taking Tenofovir monotherapy- 41 patients have ≤2000 IU/mL (80.40%), 4 patients have between 2000-5000 IU/mL (7.84%) and 6 patients have>5000IU/mL(11.76%). In 6 patients taking Entecavir monotherapy- 3 patients have ≤2000 IU/mL (50%) and 3 patients have >5000IU/mL (50%). In 3 patients taking dual therapy, 2 patients have ≤2000IU/mL (66.67%) and 1 patient has >5000IU/mL (33.33%). Among 60 patients, ADRs were reported in 41 patients (68.33%). The commonly reported ADRs were weakness, headache, dizziness, abdominal pain. The ADRs associated with Tenofovir was seen in 36 patients out of 51 patients. These are weakness (27.38%), headache (20.63%).The ADRs associated with Entecavir was seen in 5 patients out of 6 patients. These are headache (33.33%), dizziness (33.33%).

From our study it was observed that Tenofovir is having good safety and efficacy. The side effects were mild and do not impact the quality of life of the patients, whereas Entecavir is having 50% efficacy and having ADRs which are also mild in nature. Safety and efficacy of Tenofovir is much more when compared to safety and efficacy of Entecavir.

Conflict of interest

None declared

Source of funding

None declared

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