ORIGINAL ARTICLE

EFFECTIVENESS OF ENTECAVIR OR TENOFOVIR IN ERADICATING CHRONIC HEPATITIS B INFECTION IN PATIENTS WITH SUPERIMPOSED ACUTE HEPATITIS A / E VIRUS INFECTION

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ABSTRACT

Objective: To determine the effectiveness of Entecavir or Tenofovir in eradication of chronic Hepatitis B infection in patients with superimposed acute hepatitis A or E infection.

Material and Methods: This simple, non-blinded randomized controlled trial was conducted in Department of Medicine, Khyber Teaching Hospital, Peshawar and the private practice of primary author from February, 2011 to April, 2017.702 chronic Hepatitis B patients of either gender, aged between 14 and 55 were recruited in the study after fulfilling the inclusion criteria. These patients were initially chronic Hepatitis B positive, but were not started on antiviral therapy owing to low viral counts. They subsequently developed acute hepatitis (either Hepatitis A or E).60% of the patients had positive hepatitis E serology, while 40% had positive serology for hepatitis A.These patients were divided into 3 wings: 1. 281 patients were started on Entecavir 0.5mg OD; 2. 281 patients were started on Tenofovir 300mg OD; 3. 140 patients who were willing to wait for spontaneous clearance of the virus were started on liver supplements used as placebo. These patients were followed at every 4 weeks for first 3 months and then every 6 months for the next 3 years. HBsAg clearance by 3rd generation ELISA, and negative HBV PCR at 12 months was taken as End Point of the study. Results were analyzed using SPSS 23 and expressed in percentages.

Results: At the end of 6 months, 39.1% of patients started on either of Entecavir or Tenofovir achieved HBsAg clearance with negative PCR for Hepatitis B virus DNA, while only 3.3% of the placebo group achieved HBsAg negativity with negative PCR. At 12 months of initiation of treatment, 55% of patients started on either of Entecavir or Tenofovir achieved HBsAg clearance with negative PCR, while only 3.3% of the placebo group did.

Conclusion: No statistical difference was found between Entecavir and Tenofovir in the management of Acute Hepatitis in Chronic Hepatitis B patients with superimposed acute Hepatitis A / E.Both entecavir and tenofovir were statistically significant as compared to placebo in the management of Acute Hepatitis in Chronic Hepatitis B patients with superimposed acute Hepatitis A / E.

Key Words: Entecavir; Tenofovir; Chronic Hepatitis B infection; Acute Hepatitis A; Hepatitis E infection

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INTRODUCTION

The medical field has seen a recent surge in advances related to the treatment of viral hepatitis especially chronic Hepatitis C infection after the introduction of Direct Acting Anti-virals (DAAs)[1]. Acute hepatitis B is a self-limiting disease process that is usually not treated with anti-virals and only symptomatic treatment is given during the course of the disease[2]. In very few cases it can complicate into fulminant hepatitis which then carries high mortality[3-5].

Patients with chronic hepatitis B infection but low viral loads also do not qualify for anti-viral therapy[2]. But if such patients develop superimposed acute hepatitis A or E infection, it is debatable whether they should be given anti-viral therapy for eradication of hepatitis B

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virus.

We conducted this pilot study; the first of its type, to study the effectiveness of anti-viral therapy in chronic hepatitis B infected patients with superimposed acute hepatitis A or E infection. The study is based on the concept of anti-viral therapy providing immune kick to an already stimulated immune system from super-infection with hepatitis A or E infection in patients with pre-existing chronic hepatitis B, and ultimately causing eradication of hepatitis B infection.

MATERIAL AND METHODS

This simple, non-blinded randomized controlled trial was conducted in Department of Medicine, Khyber Teaching Hospital, Peshawar and the private practice of primary author from February, 2011 to April, 2017. 702 chronic Hepatitis B patients of either gender, aged between 14 and 55 were recruited in the study. An informed consent form was duly signed from all adult patients; consent for minors was taken from their parents. Permission from the Hospital Ethical Committee was also taken for conducting the study within the hospital. Patients fulfilling the following criteria were included in the study: 1. HBsAg positive and Hepatitis B Virus PCR positive; 2. History of acute Hepatitis minimum 10 days duration; 3. Serum ALT minimum 300IU; 4. Anti HAV/ HEV IgM positive; 5. Delta virus serology negative; 6. Anti HIV/HCV negative; 7. Ultrasound: Normal liver / hepatomegaly, no or minimum splenomegaly and normal portal vein; 8. Prothrombin time within 3 seconds of normal; 9. Normal renal function tests; 10.No associated vomiting / diarrhea.Patients with chronic liver parenchymal disease on ultrasound, fatty liver or diabetes mellitus were excluded from the study.

All these patients were initially chronic Hepatitis B positive, but were not started on antiviral therapy owing to low viral counts. They subsequently developed acute hepatitis (either Hepatitis A or E).60% of the patients had positive hepatitis E serology, while 40% had positive serology for hepatitis A. These patients were divided into 3 wings: 1. 281 patients were started on Entecavir 0.5mg OD; 2. 281 patients were started on Tenofovir 300mg OD; 3. 140 patients who were willing to wait for spontaneous clearance of the virus were started on liver supplements used as placebo. These patients were followed at every 4 weeks for first 3 months and then every 6 months for the next 3 years. HBsAg was repeated at every 3 months.HBsAg clearance by 3rd generation ELISA, and negative HBV PCR at 12 months was taken as End Point of the study.

Data was entered and analyzed using Statistical Package for Social Sciences (SPSS) 23. The results were tabulated in percentages, taking P value < 0.001 as statistically significant.

RESULTS

At the end of 6 months of treatment, 39.1% of the patients started on either Entecavir / Tenofovir cleared HBsAg with attainment of negative HBV PCR, while only 3.3% of the patients on placebo were able to clear HBsAg with negative HBV PCR. At the end of 12 months of treatment with anti-virals, the percentage of patients clearing HBsAg and attaining negative HBV PCR reached 55%, while it was the same 3.3.% for the placebo group.This is shown in Table 01.

Tables 2 and 3 highlight the comparison of effectiveness of entecavir and tenofovir respectively with placebo.

Table 4 highlights the comparison of efficacy of entecavir with that of tenofovir in eradicating HBV in chronic hepatitis B infected patients with superimposed acute hepatitis A or E infection.

Table 1: Comparison of Hepatitis B virus clearance with Anti-Viral therapy vs Placebo

		Drug Started						P-value
		Entecavir		Tenofovir		Placebo		
HBsAg Clearance at 6 Months	No	136	19.4%	152	21.7%	117	16.7%	<0.001
	Yes	145	20.7%	129	18.4%	23	3.3%	
PCR Status at 6 months	Negative	145	20.7%	129	18.4%	23	3.3%	<0.001
	Positive	136	19.4%	152	21.7%	117	16.7%	
HBsAg Clearance at 12 months	No	81	11.5%	95	13.5%	117	16.7%	<0.001
	Yes	200	28.5%	186	26.5%	23	3.3%	
PCR Status at 12 months	Negative	200	28.5%	186	26.5%	23	3.3%	<0.001
	Positive	81	11.5%	95	13.5%	117	16.7%	

Table 2: Comparison of effectiveness of entecavir with placebo

		Drug Started				
		Entecavir		Placebo		P-value
HBsAg Clearance at 6 Months	No	136		117	27.8%	<0.001
	Yes	145	<0.001	23	5.5%	
PCR Status at 6 Months	Negative	145		23	5.5%	<0.001
	Positive	136	<0.001	117	27.8%	
HBsAg Clearance at 12 Months	No	81		117	27.8%	<0.001
	Yes	200	<0.001	23	5.5%	
PCR Status at 12 Months	Negative	200		23	5.5%	<0.001
	Positive	81	<0.001	117	27.8%	

Table 3: Comparison of effectiveness of tenofovir with placebo

		Drug Started				
		Tenofovir		Placebo		P-value
HBsAg Clearance at 6 Months	No	152	36.1%	117	27.8%	<0.001
	Yes	129	30.6%	23	5.5%	
PCR Status at 6 Months	Negative	129	30.6%	23	5.5%	<0.001
	Positive	152	36.1%	117	27.8%	
HBsAg Clearance at 12 Months	No	95	22.6%	117	27.8%	<0.001
	Yes	186	44.2%	23	5.5%	
PCR Status at 12 Months	Negative	186	44.2%	23	5.5%	<0.001
	Positive	95	22.6%	117	27.8%	

Table 3: Comparison of efficacy of Entecavir to that of Tenofovir in eradicating Hepatitis B Virus

		Drug Started				
		Entecavir		Tenofovir		P-value
HBsAg Clearance at 6 Months	No	136	24.2%	152	27.0%	0.17
	Yes	145	25.8%	129	23.0%	
PCR Status at 6 Months	Negative	145	25.8%	129	23.0%	0.17
	Positive	136	24.2%	152	27.0%	
HBsAg Clearance at 12 Months	No	81	14.4%	95	16.9%	0.2
	Yes	200	35.6%	186	33.1%	
PCR Status at 12 Months	Negative	200	35.6%	186	33.1%	0.2
	Positive	81	14.4%	95	16.9%	

DISCUSSION

Results of the current study reveal that anti-viral therapy is more efficacious than placebo in eradicating chronic hepatitis B infection in patients with superimposed acute hepatitis A or E infection. However, neither of the two anti-virals is superior to the other one in effectiveness of cure. Since this is the first study of its type, literature is relatively scarce regarding this therapeutic approach for eradication of Hepatitis B Virus.

Acute hepatitis A and E are relatively common in Pakistan. Multiple factors are responsible for this occurrence; top and the foremost being lack of awareness in the masses about these infections and non-availability of free hepatitis A vaccine[6,7]. Poor sanitary conditions and inappropriate disposal systems also contribute to the high incidence of acute hepatitis A and E infections[8-10]. Since the incidence of hepatitis A and E is on the rise, it is also being seen in patients

who are already suffering from chronic hepatitis B infection[11].Since chronic hepatitis B and C carry a high prevalence in China, Taiwan and other countries of Asia and Africa, most of the studies on the epidemiology of these infections, and associated complications, manifestations and superinfections have also been conducted in these countries. Epidemiological studies from China found a superinfection rate of 32.4% with 2 or more viruses. 41.2% of CHB patients were superinfected with HAV, while 17.6% were superinfected with HEV1-3. China and South Asia carry HAV and HEV as endemic infections; these are also the most common causes of acute hepatitis in this part of the world[12]. The viruses generally lead to an acute and self-limiting infection that does not require any specific treatment and usually subsides on its own, with no subsequent morbidity[13-14]. Recent literature reveals that both HAV and HEV infections can lead to severe disease that can even complicate into fulminant hepatitis and therefore high potential risk of mortality[15]. The incidence of fulminant hepatitis increases in patients who are already suffering from chronic liver disease[16]. Prior data on the occurrence of HAV and HEV in CHB patients is scarce and no previous comparative studies of patients with the twosuperinfections are available. However, some work in the field has revealed that HBV/HEV coinfection is more fatal than HBV/HAV coinfection[17]. It is therefore important to prevent patients with pre-existing CHB infection from getting coinfected with either of HAV or HEV infections. This can be achieved by taking measures such as consuming boiled water, avoiding intake of raw or improperly cooked food, and implementing vaccination against hepatitis A infection[18-20].

Immunologic mechanisms are responsible for HAV-related liver disease. Direct toxicity of HAV is not considered to be causative[21]. It is postulated that during HAV/HBV coinfection, INF-γ produced in response to HAV has an antiviral effect on the HBV. This leads to reduced hepatitis B viral replication in patients superinfected with HAV and can even cause clearance of the chronic hepatitis B infection[22-25]. But, since adecline in HBV viral load leads to increase in immune response of the host, sometimes the excessive host response may cause severe damage to hepatocytes even to the extent of fulminant hepatitis[26].

Some studies have reported no difference between the clinical manifestations and severity of disease of HAV/HBV coinfection and HAV alone[27-28].Since HAV/HBV and HEV/HBV coinfections are a topic of recent interest, some varying literature is seen regarding the work of different studies on the issue[29-30]. The largest case series reported an outbreak of hepatitis A in Shanghai in 1988, in which 310,746 cases were reported with a fatality rate of 0.015%. HBsAg positive cases as calculated from 8.8% HBsAg carrier rate in this region of China carried 6.2 fold greater mortality than patients without HBV infection1-3. However, in the majority of cases it is hard to determine the state of the HBsAg carrier (for example healthy carrier, chronic hepatitis, or liver cirrhosis) at the time of treatment for acute hepatitis A, because in most cases the state of their liver has not been regularly checked[31-32].

All the studies conducted so far have focused on the clinical manifestations and complications of HAV/HBV and HEV/HBV coinfections 1-3. So far we have not come across any study regarding the therapeutic approach to management of acute hepatitis A or E superinfection in patients with chronic hepatitis B infection. Our study has mainly concentrated on treatment of chronic hepatitis B infection with anti-viral therapy in patients who were previously not eligible for treatment due to low viral loads but were subsequently started following the hypothesis that anti-viral therapy initiation in such patients superinfected with acute hepatitis A or E infections may cause rapid clearance of hepatitis B virus.

LIMITATION OF STUDY

To the best of our knowledge, since this is the only study conducted on the topic, further multi-center studies are needed before we can come up with any recommendations for future management of such patients.

CONCLUSION

There was no statistical difference between the effectiveness of Entecavir and Tenofovir in the management of Acute Hepatitis in Chronic Hepatitis B patients with superimposed acute Hepatitis A / E. However, both entecavir and tenofovir were statistically significant as compared to placebo in the management of Acute Hepatitis in Chronic Hepatitis B patients with superimposed acute Hepatitis A / E.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Humayun M: Main idea, Data collection and Overall supervision
Badshah A: Data Analysis
Haider I: Literature Search

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.