Mortality Rate in HBV Reactivated Patients with Direct Acting Antivirals for Treatment of HCV

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***Abstract*-** Lack of studies showing the risk of HBV reactivation in patients treated with direct acting antivirals (DAAs) for hepatitis C virus. Eleven patients among 158 were positive for HBV who received direct-acting antivirals (DAAs) in various hospitals of Punjab, Pakistan. The reactivation of HBV established when viral DNA level ≥100 IU/mL in serum and higher ALT level was set as 2 times increase in normal level. The others parameters like Hemoglobin, White Blood Cells and Platelets were monitored respectively. The sofosbuvir/daclatasvir based therapy was used in seven cases while sofosbuvir/ ledipasvir in four cases. When reactivation of HBV occurred in these cases, although the effective response initially noted against HCV but no response at later stage, it led to death in four patients. The variation of ALT level showed the reactivation of HBV in these cases. When no sufficient response with DAAs was achieved in HCV patients, there would be reactivation of hepatitis B virus that is a major health concern.

***Index Terms*-** Alanine aminotransferase, Direct Acting Antivirals, Hepatitis B virus, Hepatitis C virus

I. Introduction

Direct-acting antivirals (DAAs) have completely changed the appearance of HCV infection. Current treatment regimens can eliminate viral hepatitis infection nearly in all patients, with an excellent safety profile. Among the few possible side effects, hepatitis B virus (HBV) reactivation has been reported in patients with HCV and HBV treated with DAA (Wang et al., 2017). Hepatitis C virus infection can now be treated in almost all patients with these effective, well-tolerated formulations of oral DAAs. Even those who were not eligible for IFN treatment associated with patients with advanced liver disease or patients with comorbidity, or those who had failed treatment, now have ideal treatment options (EASL, 2014). The hepatitis B virus reactivation is characterized by the unexpected increase in HBV DNA levels in patients with inactive or previously resolved HBV infection (Londoño et al., 2017). However, the occurrence and clinical features of HBV reactivation following IFN-free DAA for HCV have not been fully addressed by prospective studies. Therefore, we aim to evaluate the risk of HBV reactivation in patients who received IFN-free DAA for HCV.

II. Materials and Methods

The five hundred and fifty-eight chronic hepatitis C patients who received Interferon free DAAs for hepatitis C virus from different hospitals of Punjab enrolled in this study. Patients with age ≥20 years with chronic HCV infection (Abbott HCV EIA 3.0 method), High viral load of HCV (AJ Roboscreen, Germany; quantification limit 25 IU/mL), serum ALT and treatment-resistant cases were included. Co-infected cases like HBV and HIV were excluded. Treatment was given as approved criteria for sofosbuvir-based therapy. Reactivation of hepatitis B virus was considered when serum HBV DNA ≥100 IU/mL. All patients under treatment visit regularly and all laboratory parameters assessed at each visit. Required statistical parameters like mean, percentage, standard deviation, SE mean, CI 95% were used and results showing P-value <0.5 were considered significant. This study was approved by the institutional (University of Gujrat, Punjab, Pakistan) ethical committee and conducted according to Helsinki Declaration. Written informed consent was taken from all patients before participating in the study.

III. RESULTS

In this study, we included 158 cases with mean age 43±13 years. The major laboratory parameters of HBV infected patients (n=11) are mentioned in Table 1.

Table 1. Laboratory Parameters of Infected Patients

Patient	Age	Sex	PCR	SVR	HBsAg	WBCs	PLT
1	51	F	3790850	No	No	8.7	178
2	34	M	11979	Yes	No	4.3	245
3	36	M	4100	Yes	No	5.1	350
4	45	F	9980	Yes	No	4.8	326
5	57	M	29590	Yes	No	7.0	225
6	68	M	26500	Yes	No	5.6	411
7	29	M	703225	No	No	4.0	222
8	35	M	413560	Yes	No	9.2	390
9	55	F	887050	No	No	4.1	271
10	25	M	37800	Yes	No	5.5	242

11	39	F	127600	No	No	4.6	388

PCR=Polymerase Chain Reaction; SVR=Sustained Virolgical Response; HBsAg= Hepatitis B surface Antigen; WBCs=White Blood Cells; PLT=Platelets

The frequency of males patient was higher (64%) compared to female (36%). Sustained virological response (SVR) was noted in 92% of treated patients, while 8% of treated patients had recurrence as shown in Table 2.

Table 2. Data of Enrolled Cases in the Study

Population based data		**Values**
Age		43±13 years
Sex	Male	101
	Female	57
SVR after 12 week of DAAs	Responsive	145
	Recurrence	13

The mean HCV viral load was 549294 IU/ml for HBV patients and 489628 IU/ml for non-infected patients. All patients were infected with HCV genotype 2b. The eight cases showed the reactivation of HBV just after six weeks of DAAs therapy. Later on, two cases after twelve weeks and one case after six months. Seven cases achieved the SVR during 12 weeks and four cases did not achieve SVR even after one year as indicated in Table 3.

Table 3. Frequency and Response time of Direct Acting Antivirals

Treatment timeline	**Cases**
Within 6 weeks of therapy	8
After 12 weeks of therapy	2
After 6months of therapy	1
Total	11
SVR Respond to therapy No response	 7 4

The mean ALT level decreased after treatment with *P*-value 0.007, showed that DAAs efficiency was highly significant within a short duration of time (1 month). Variation in ALT level was an important parameter for a liver condition. DAAs lead to a decrease in hemoglobin level and WBCs in the first four weeks of treatment significantly. The cells of Immune-related response were decreased strongly (P=0.000) with the use of DAAs. There was a unique and different scenario in the case of viral RNA level that decreased to lower the detectable limit (< 25 IU/Ml), no difference was seen after the treatment as all patients clear the virus using oral therapy. Hence, *P*-value was above (0.100) the set level of significance (Table 4).

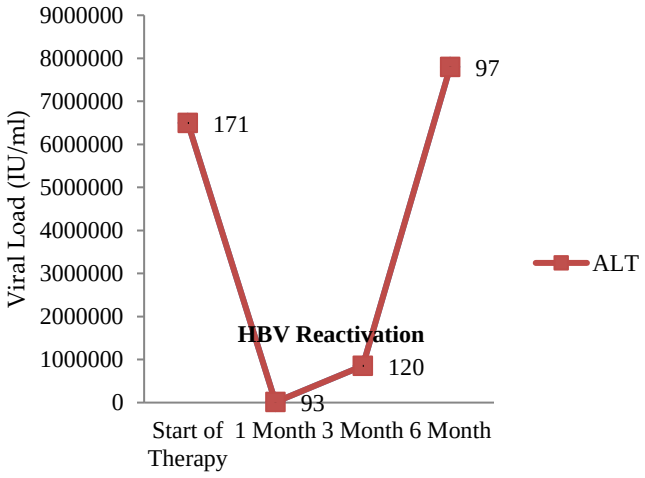
Table 4. Data of before and after use of DAAs therapy for 1 month

Parameters		**Mean**	**Std. Dev**	**SE Mean**	**95% CI**	**T value P value**
					Lower Upper	
ALT	BT	77.91	29.14	8.79	8.65 42.62	3.36 0.007
	AT	52.27	10.14	3.06		
HB	BT	12.082	1.154	0.348	0.383 2.363	3.09 0.011
	AT	10.709	0.997	0.301		
WBC	BT	7.609	1.804	0.544	0.993 2.371	5.44 0.000
	AT	5.927	1.222	0.368		
Viral RNA	BT	979256	1794286	540998	-226161 2184674	1.81 **0.100**
	AT	0	0	0		

ALT= Alanine Aminotransferase; HB= Hemoglobin; WBC= White Blood Cells; BT= Before Treatment; AT= After Treatment

The reactivation of HBV was directly associated with SVR and variation in liver enzyme after Direct Acting Antivirals treatment for HCV. Initially, the average viral load of selected cases (n=11) was greater than 6million IU/ml, which reduces significantly using DAAs for one month. On the other hand, the average ALT level also reduced from 171 to 93. The Sudden increase in ALT (121) and viral load (>1million IU/ml) was noted after 3 months of therapy in these cases with reactivation of HBV. No significant response was found after reactivation of HBV in these cases until six months of continuous prescribed therapy (Figure 1). Four among eleven of these patients died after one year.

Figure 1. Effect of DAAs on ALT and Viral Load and timeline of HBV reactivation



IV. DISCUSSION

Our study showed severe hepatitis B reactivation during DAAs therapy in the treatment of HCV infection. Many studies had shown the association between DAAs treatment (and rapid drop in HCV viral load) with the reactivation of underlying viral infection such as HBV (Londoño et al., 2017; Perelló et al., 2016). Reactivation of HBV occurred in 8% of cases with DAA treatment in our study. In contrast, the latest study mentioned that 9 % of patients who received the DAA treatment had HBV reactivation and only 1 to 4% of patients resolved HBV (Mücke et al., 2018). Another study reported that 7.7% of cases were positive for Hepatitis B virus among 104 cases infected with HCV and treated with DAAs (Calvaruso et al., 2018). The frequency of infection was higher in male (64%) as compared to female (36%) patients and SVR was not achieved after six months in 36% cases (n=11). HBV reactivation depends on the SVR and ALT variation when treatment duration has been completed for HCV. Four among eleven patients did not achieve the SVR after one-year use of DAAs and ultimately lead to death. A meta-analysis published that 29.8% of patients had an increase in HBV viral load, eight showed HBV reactivation and six had peak ALT levels (Chen et al., 2017). The patients were properly observed who showed the reactivation of HBV after 4 weeks and subsequent increase in ALT level defined as reactivation of HBV and negative HBsAg, Our findings are similar to Wang et al. 2017. Except for ALT level, no important parameter showed this reactivation of HBV.

Several studies were published related to HBV reactivation in co-infected patients (HCV/HBV) treated with DAAs. Still the rate of reactivation is unclear and ALT flares lead to liver damage and even death. These results are in line with Macera et al. 2017. In other cases, IFNs have an antiviral effect of declining replication of HBV and delaying HBV reactivation (Lau et al., 2005) as DAAs did not show any effect on the innate immune response. Significant treatment outcomes for chronic HCV patients with DAAs therapies and these treatment leads to HBV reactivation and recent data published in various studies supporting our finding (Collins et al., 2015; Ende et al., 2015). The AASLD guideline recommended the anti-HBV treatment for active HBV infection (AASLD, 2016). In contrast, the European Association for the Study of the Liver (EASL) guideline recommended that the patients with HBsAg positive treated with direct- acting antivirals should receive simultaneous antiviral prophylaxis minimum of 12 weeks after DAAs therapy (EASL, 2017).

V. CONCLUSION

Based on the HBV reactivation with IFN free antivirals and flare of ALT, there is strong relationship. We advise a high ranking of clinical suspect cases for early identification and management. The achievement of SVR after DAAs therapy and risk of HBV reactivation confirmed based on the recurrence of HBV after DAAs due to immunity alteration. These finding highlight the significance of HBV diagnosis before initiating DAAs treatment, requiring keen monitoring of HBV reactivation during treatment and timely use of anti-HBV treatment to prevent further death. The HBV reactivated patients need attention because it can be incurable once it occurs. Additional studies are requisite.

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