

Reactivation of herpesvirus in patients with hepatitis C treated with direct-acting antiviral agents

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Background: We performed a case-series analysis of reactivation of herpesvirus in patients with hepatitis C virus (HCV) infection treated with direct-acting antiviral (DAA) agents.

Methods: Eight cases were detected among 100 treated patients with DAA regimens in Qena University Hospital from June 2016 to June 2017. Herpesvirus was reactivated in eight patients who received DAA therapy. None of the cases had risk factor for herpes zoster reactivation.

Results : The DAA regimens used were sofosbuvir/daclatasvir in six cases and sofosbuvir/ledipasvir in two cases. Immune changes that follow HCV clearance might lead to reactivation of other viruses, such as herpesvirus.

Conclusion: Patients with HCV infection suspected of having herpesvirus infection should be treated promptly.

Keywords: HCV, HZ, DAA

Introduction

The development in hepatitis C virus (HCV) drug therapy in the last few years has led to the evolution of antiviral treatment for HCV with progression from interferon (IFN) to the direct-acting antivirals (DAAs).¹

HCV infection can now be treated in almost all patients with these well-tolerated and effective combinations of oral DAAs. Even those patients who were not eligible for treatment by pegylated IFN-based regimens as in the case of patients with advanced liver disease or patients with comorbidities, or those who failed treatment, now have perfect choice of treatment modalities.²

Perelló et al reported herpesvirus (HV) reactivation in patients with HCV infection treated with DAA therapy.³

Immune system changes that occur after starting DAAs could play a role in HV reactivation. However, the exact mechanisms involved in HV reactivation in the early phases of HCV clearance in patients treated with DAAs are not clear.⁴

Patients and methods

One hundred chronic hepatitis C patients attending the outpatient clinics of the Tropical Medicine & Gastroenterology and the Internal Medicine Departments, Qena University Hospital were included in the study. All eligible patients were included according to the inclusion criteria approved by the National Committee for Control of Viral Hepatitis: age 18–75 years, HCV RNA positivity, any BMI (weight in kilograms/squared height in meters), and only treatment-naïve patients were included in this study. Exclusion

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criteria included hepatitis B virus (HBV) coinfection, HIV, decompensated liver cirrhosis, inadequately controlled diabetes mellitus (HbA1c >9%), hepatocellular carcinoma, or extrahepatic malignancy. Diagnosis of liver cirrhosis was on clinical basis involving laboratory tests and ultrasonography findings of liver cirrhosis and/or liver stiffness measurement ≥ 12.5 kPa.⁵

Patients were subjected to history taking, clinical examination, and routine laboratory workup. All patients were treated with sofosbuvir-based treatment regimens according to the approved treatment recommendations. The study was approved by the ethical committee of Qena Faculty of Medicine-South Valley University. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before treatment.

Results

We present the baseline characteristics of the eight herpes zoster (HZ) infected patients in Table 1.

Our study included 100 patients with mean age 45 ± 12 years. Males were predominant, constituting 69% of our cases. Eighty percent of cases were noncirrhotic at the start of treatment and 20% of patients had evidence of liver cirrhosis. Sustained virologic response (SVR) was found in 94% of treated patients while 6% of the treated patients relapsed (Table 2).

Mean FIB-4 score for noninfected patients was 4.5 ± 2.5 and for HZ patients it was 3.35. Mean HCV RNA level was 569,000 IU for HZ patients and 685,230 IU for noninfected patients. All patients were HCV genotype 4. No medications

were reported for treatment of any comorbidities in our studied patients.

In the first 2 months after starting DAAs, we encountered four noncirrhotic cases with vesicular eruptions varying in distribution with two patients having vesicles over right side of the chest and two patients having the vesicles extending to the upper back. A diagnosis of HZ was made after consultation with a dermatology consultant who prescribed antiviral and analgesics. All patients achieved SVR.

After 6 months of treatment with DAAs, three cases (two noncirrhotics and one case with compensated cirrhosis) had maculopapular vesicles on an erythematous base over the right hemithorax. HZ diagnosis was established and confirmed by the dermatologist. Of the three cases, only one case had SVR.

Table 2 Demographic data in the studied group

Demographics	(Mean \pm SD, n %)
Age, mean \pm SD	45 \pm 12
Sex, (%)	
Male	69
Female	31
Presence or absence of baseline cirrhosis, (%)	
Noncirrhotic	80
Cirrhotic	20
Response at 12 weeks after EOT (SVR12), (%)	
Sustained responders	94
Relapsers	6

Abbreviation: SVR, sustained virologic response; EOT, end of treatment.

Table 1 Baseline characteristics of the infected patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age	51	44	52	60	43	49	63	50
Sex	M	F	F	M	F	F	F	M
DM	N	N	N	N	N	N	N	N
Previous treatment	N	N	N	N	N	N	N	N
LTx	N	N	N	N	N	N	N	N
Ttt	SOF/DAC	SOF/DAC	SOF/DAC	SOF/LED	SOF/DAC	SOF/LED	SOF/DAC	SOF/DAC
HBs Ag	N	N	N	N	N	N	N	N
SVR	Y	Y	N	Y	N	N	Y	Y
PCR	3,000	151,000	582,000	1,532,001	2,563,987	245,300	98,560	96,523
Immunosuppression	N	N	N	N	N	N	N	N
FIB-4	1.5	8	0.95	5.2	7.3	2.5	1.9	4.2
WBC	4	5	4.2	5.3	8	7.3	6.8	9
PLT	210	300	180	420	240	350	330	280
Ocular	N	N	N	N	N	N	N	N
Complications								
Reactivation	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Cutaneous	Cutaneous

Abbreviations: Ag, antigen; DAC, daclatasvir; DM, diabetes mellitus; FIB-4, fibrosis 4; HBS, hepatitis B surface; LTx, liver transplant; PLT, platelet; SOF, sofosbuvir; SVR, sustained virologic response; Ttt, treatment; WBC, white blood cell.

After 1 year of treatment, a case with compensated cirrhosis developed vesicular rash on the right costal margin and was diagnosed as HZ after dermatology consultation. The case did not achieve SVR.

Liver enzyme changes together with WBC, neutrophils count, and HB level before, during, and upon reactivation of HZ are summarized in Table 3.

We found that HZ reactivation was significantly associated with achievement of SVR after DAA treatment for HCV ($P=0.000$) but no significant association between liver condition and HZ reactivation was found (Table 4).

Discussion

Bacterial infections were relatively common among HCV patients treated by IFN, especially with advanced liver disease.^{6,7} With new DAA, infectious complications do not appear to be a problem in this setting. The HV family is known for its ability to establish life-long infection.⁸

HZ is the result of reactivation of a previous varicella-zoster virus (VZV) infection, remaining latent in cranial nerves and dorsal root ganglia and manifesting when there is immune system suppression.^{8,9} However, balance between latency and reactivation of VZV seems to be a complex process in which a precise understanding of the activated pathways by clinical factors is lacking.⁸

Our study was conducted in 100 HCV patients attending the outpatient clinic of Qena University Hospital. During a follow-up period of 1 year of these patients, we encountered eight cases of cutaneous HZ reactivation during DAA treatment with no postherpetic complications. There were no risk factors for HZ reactivation, no posttransplantation states, no physical stress, no immunocompromised status, and none of the patients were known to have diabetes or HIV infection. Of the eight cases, two patients were cirrhotic, and the remaining were noncirrhotic patients. We found that HZ reactivation was significantly associated with achievement of SVR and the liver condition had no role in HZ reactivation.

The same findings of HZ reactivation were reported in a recently published series of 10 cases out of 576 (2%) HCV patients treated with DAAs. The mean age of these patients was 67 years and three of them were receiving immunosuppressive therapy following liver transplantation.³

No evidence of HBV infection reactivation was encountered after DAA treatment of our HCV patients.

Suppressive effect of HCV infection on HZ that is removed after treatment by DAAs could be assumed as the main reason for HZ reactivation or may be a possible direct role of DAAs as a part of immune system restoration.¹⁰ Another explanation may be immune reconstitution inflammatory syndrome (IRIS), which can be seen in some HIV-infected patients after highly active antiretroviral therapy. This syndrome implies a pathologic inflammatory response to previously acquired conditions in the setting of an improved immune response, with mucocutaneous HZ being one of them. IRIS can happen even several months after initiation of highly active antiretroviral therapy.¹¹

Conclusion

Even when a causal relationship is not confirmed, based on the temporal association and recent experience, we conclude

Table 4 Herpes zoster reactivation after direct-acting antiviral treatment

Disease	Number of patients	P-value
Baseline infected	0	
First 2 months from start of treatment	4	
After 6 months from start of treatment	3	
After 1 year from start of treatment	1	
Total number of infected patients	8/100	
Sustained virologic response		
Responder	5	0.000
Nonresponder	3	
Cirrhotic patients	2	0.201
Noncirrhotic patients	6	

Table 3 Laboratory data for herpes zoster–infected patients before and after direct-acting antiviral treatment

	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Case 8	
	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT
ALT	44	32	45	34	41	36	45	28	55	30	58	52	49	41	48	20
AST	35	29	34	28	32	30	31	22	43	40	38	36	42	39	47	21
HB	13	14	13.5	13.6	12.5	13.1	13.3	15	13.1	14.2	12.8	13	12.8	13	11.9	13.8
WBC	7	6.2	6.5	7	5.5	7.5	5.3	7	5	5.2	3.5	6.8	5.2	5	4.7	7.3
Neutrophils	4	5.5	3.5	6.4	3.3	4.2	2.8	6.5	4	6	1.9	2.8	2.3	3.1	3.9	5.6
HCV RNA	3,000	0	151,000	0	582,000	1,100	1,532,001	0	2,563,987	0	245,300	12,500	98,560	0	96,523	0

Notes: Bold values are significant of SVR as a risk factor for HZ reactivation.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT after treatment; BT, before treatment; HB, hemoglobin; HCV, hepatitis C virus; WBC, white blood cell.

that IFN-free regimens may be associated with increased incidence of HV reactivation, but more cases are required to confirm these findings. Also, we advise a high grade of clinical suspicion for early recognition and management of these cases. SVR achievement after DAA treatment and risk of HZ reactivation is not confirmed based on our small number of cases but it may give a clue to possible occurrence of HZ reactivation after DAAs due to immunity alteration, so high index of clinical suspicion may be needed to guarantee early and prompt management of such cases but more cases are required to prove that association.

Acknowledgments

This abstract of this paper was presented at the APASL Conference 2018, March 14–18, as a poster presentation with interim findings.

Disclosure

The authors report no conflicts of interest in this work.

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