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Cerebrovascular Accident; a Possible Serious Adverse Event of Combined Sofosbuvir-Daclatasvir Therapy: A Case Report

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Abstract

Introduction: *Combined sofosbuvir- daclatasvir therapy is considered one of most effective and tolerable regimens in treating chronic hepatitis C. both are pan-genotypic and ideally used for either three or six months with or without ribavirin. Insomnia, headache and fatigue are the most commonly reported adverse effects with little serious adverse events and only one reported case with cerebrovascular accident after this regimen in a patient with evident risk for hypercoagulability.*

Case presentation: *We report a case of ischemic stroke as a possible serious adverse event during three months course of combined sofosbuvir-daclatasvir therapy in a 68 years old Egyptian female. Our patient had no risk factors for hypercoagulability and suddenly complained left side hemiplegia that proved radiologically to be due to large right cerebral recent ischemic infarction.*

Conclusion: *Although our case is the first reported stroke in non-risky chronic hepatitis C patient during three months combined sofosbuvir-daclatasvir therapy, we recommend close neurological monitoring during this regimen.*

Keywords: *sofosbuvir, daclatasvir, chronic HCV, stroke, cerebrovascular*

1. Introduction

The current treatment of chronic hepatitis C infection is based on various direct-acting antiviral (DAAs) oral regimens that show increased SVR rates, favorable tolerability, shortened treatment duration, low rates of serious intolerable adverse events of INF-α based therapy or discontinuation of therapy (1-3). New HCV treatment guidelines consists of combinations of drugs, and therefore efficacy and safety are mostly evaluated in patients using combination therapy, making data hard to interpret for only one drug (4).

Both sofosbuvir (SOF) and daclatasvir (DCV) are pan-genotypic DAAs and used as an ideal 3 months or 6 months management protocol for non-cirrhotic or cirrhotic HCV patients respectively (3, 5). Most commonly reported adverse events for SOF-DCV combined therapy are insomnia (30 %), headache (24 %), and fatigue (20 %) (4). Infrequent serious adverse events were reported during or after the treatment period (6).

We observed a stroke as a serious adverse event during treatment with SOF-DCV combined regimen for an old Egyptian female with no risk factors for hypercoagulability. The full historical data, examinations, full investigations, and management protocol are presented.

2. Case Presentation

A 68 years old chronic HCV infected female , not known to be diabetic nor hypertensive, presented to outpatient clinic propped by her relatives with acute onset weak flaccid both left upper and lower limbs, lost knee, ankle reflexes and planter response, and hemi-hypoesthesia of the left side of body in addition to mild dropping of right angle of the mouth. There was no past history of similar attacks or any episodes of loss of consciousness before. Her chronic HCV infection was diagnosed since about 8 years. Our patient was fully conscious, oriented to time, place and persons. Her ABP was 110/70, 62 bpm regular pulse, temperature 36.9 ^{o}C, average weight, not bedridden and was on her ordinary daily activities. No signs of dehydration or any other abnormalities were detected on general examination. Abdominal ultrasonography showed non-cirrhotic coarse liver texture, mild splenomegaly and no ascites.

Regarding drug history; only multivitamins, H2 blocker and propranolol were prescribed months ago. In addition to SOF/DCV combined therapy for her chronic HCV since 28 days in a three months regimen.

Her basal laboratory results at zero point for HCV treatment showed HCV antibody positive, HCV RNA 7290162 IU/ml, HB 12 g/dl, platelets 173000/mm^3, SGPT 93 U/L, SGOT 79 U/L, serum albumin 3.56 g/dl, total bilirubin 0.8 mg/dl, serum creatinine 0.9 mg/dl, fasting and 2 hours post prandial were 89-107 mg/dl respectively, no proteins or casts were detected in urine, AFP 19.1 mg/ml.

ECG showed regular sinus rhythm at rate 60 bpm with no ischemic changes. Non-contrast MRI of brain using multiple pulse sequences in different planes revealed right cerebral recent ischemic infarction in the territory of the right MCA that was described as a large fairly defined area of abnormal S1 seen at the right cerebral hemisphere (temporo-parietal with small extension into frontal and occipital regions). It displays low S1 on T1 and high S1 on both T2 & FLAIR images. On diffusion study, it displays high S1 on b1000 DWIs and low S1 on ADC map (restricted diffusion). No related mass effect. And another similar lesion was seen at the right deep frontal region.

Neurological consultation confirmed the evidence of stroke and advised LMWH and maintenance on antiplatelet in addition to physiotherapy and we advised to stop propranolol and the combined SOF/DCV therapy for this serious adverse event but the patient refused stoppage her anti-HCV drugs especially after undetectable viraemia at one month treatment.

Almost all investigations to detect possible risk of hypercoagulability were asked and showed A positive blood grouping, D-dimer 320 ng/ml (normal less than 250), LDH 1307 U/L (normal 225-450 U/L), negative coombs test, serum cholesterol and triglyceride were 165 & 130 respectively, protein C & S were 71% & 83% respectively (normal 70-140%), lupus anticoagulant 43 sec (normal 34-43 sec), Anti thrombin III 19.1 mg/l (normal 19-31 mg/l), negative both anti-cardiolipin IgG & IgM, APTT 25 sec (normal 25-37 sec), ANA & anti ds-DNA were negative.

Our patient also showed excellent response regarding anti-HCV combined SOF/DCV therapy where undetectable HCV PCR was noticed at 4^{th} week of therapy, continue her anti-HCV drugs with close monitoring. On further follow up of our patient, she achieved undetectable viraemia also at the end of 3 months treatment, acquired considerable motor functions for her limbs on neurological supportive treatment and physiotherapy with no recurrence of any cerebrovascular events.

3. DISCUSSION

Our 68 years old female was known chronic HCV patient with no significant history of medical diseases known to be risk factors for hypercoagulability or cerebrovascular accident. Her basal laboratory findings denoting her compensated liver state without laboratory or sonographic evident cirrhosis with Fib 4 equals 3.22 and APRI equals 1.3 denoting the degree of fibrosis as F2 and hence the prescribed combined SOF/DCV regimen for her chronic HCV.

After entering hepatocytes, the viral genome of HCV is translated into a single polypeptide which is subsequently cleaved into viral proteins that are essential for HCV replication and viral assembly. SOF inhibits NS5B RNA dependent RNA polymerase and DCV is an inhibitor of NS5B, both inducing disruption of viral replication (1, 2).

SOF is administered at 400 mg/day then metabolized intracellular and forms the active metabolite GS-461203, followed by dephosphorylation resulting in the inactive compound GS-331007 which is primarily renally excreted. SOF is 61–65 % bound to plasma proteins. GS-331007 is minimally bound to plasma proteins (4).

DCV is a first-in-class HCV NS5A replication complex inhibitor (1, 2), administered at a dosage of 60 mg/day, highly bound to plasma proteins (99 %), hepatically metabolized (CYP3A4), and biliary excreted (2, 4, 7).

SOF was in general well-tolerated even in patients with advanced cirrhosis and in dialysis-dependent patients. There was no evidence of an elevated risk of SOF-related toxicity in CKD patients. Also, no cardiac toxicity was reported (4).

DCV is well tolerated, even in combination with SOF (8). Most commonly reported adverse events for SOF-DCV combined therapy are insomnia (30 %), headache (24 %), and fatigue

(20 %) (4). Less commonly nausea, anemia, diarrhea (<10%) and transient increase in serum lipase (4, 7, 8).

More adverse events are reported if we add ribavirin (RBV) to SOF-DCV combined therapy with more incidence of anemia (20 %), nausea (17 %), rising total bilirubin 2.5 folds ULN (15 %), lymphopenia <0.5 x 10^9/l (10 %) (4).

Infrequent serious adverse events were reported during the treatment period included single events of gastroenteritis, colitis, stroke, acute renal failure from dehydration that resolved with administration of fluids, forearm fracture, anxiety and pleuritic pain, exacerbation of psoriasis, and hypokalemia (6).

Reported discontinuation of treatment because of serious adverse events was also infrequent (5, 6). A naïve female discontinue DCV+SOF+RBV×24weeks regimen for HCV genotype 2 at weak 12 due to fibromyalgia exacerbation occurred at weak 10 (6). Two cases reported treatment discontinuation due to extreme bradycardia after first doses of SOF and DCV in patients receiving amiodarone with or without propranolol (5). Some authors showed no serious adverse events even in treating cirrhotic child class B/C patients (4).

The only reported ischemic stroke after combined SOF/DCV was 54 year-old white naïve male with prior history of smoking, hyperlipidemia, hypothyroidism, myocardial infarction, and a family history of stroke denoting significant risk factors for hypercoagulability. He experienced a cerebrovascular accident at week 22 of DCV+SOF×24 weeks regimen for HCV genotype 1a. Study therapy was discontinued and the patient entered follow- up. The patient achieved SVR24 (6).

Regarding our case; we investigated our patient to exclude any possible acquired risk factors of hypercoagulability. Absence of any family history of stroke, non hypertensive nor diabetic, normal lipid profile and absence of ischemic changes in ECG exclude some of risk factors. Exclusion of hereditary hypercoagulability was done by normal laboratory test as protein C & S, anti-thrombin III and normal wild type factor V Leiden. Exclusion of hemolysis, dyslipidemia, systemic lupus and anti-phospholipid syndrome also were done. High D-dimer and LDH levels confirm presence of ongoing thrombosis. So, we reported the first stroke case possible to occur after combined SOF/DCV therapy for chronic HCV.

Stoppage of propranolol due to bradycardia (5) and to avoid risk of cardiac arrest (3) with absence of evident indications for its prescription, continuing SOF/DCV therapy after a discussion with our patient, supportive neurological treatment, antiplatelet, and physiotherapy were recommended. No drug-drug interactions reported between the ongoing anti HCV therapy and previously or recently recommended regimen for our patient (online HEP Drug Interaction Checker).

Excellent non-detectable HCV PCR response was noticed at 4th week of SOF/DCV therapy and better neurological and motor improvement were obtained. Undetectable viraemia at end of chronic HCV treatment was obtained with no recurrence of any cerebrovascular events that may be explained by adding antiplatelets to our regimen.

Up to our knowledge, we search for literature and did not find a possible direct mechanism explaining this serious ischemic cerebrovascular accident after any of combined SOF/DCV therapy. This could be explained by still recent drugs with no much related researches in this topic.

4. Conclusion

Unexplained ischemic cerebrovascular accident may be a possible serious adverse event of the pan-genotypic combined SOF/DCV therapy of chronic HCV even in absence of hypercoagulability risk factors. Close neurological monitoring of these HCV patients on this regimen is recommended.

5. Abbreviations

DAAs: Direct-acting antiviral, **INF-α:** Interferon alpha, **HCV:** hepatitis C virus, **SOF:** sofosbuvir, **DCV:** Daclatasvir, **RBV:** Ribavirin, **ABP:** Arterial blood pressure, **HB:** Hemoglobin, **SGPT:** Alanine transferase, **SGOT:** Aspartate transferase, **AFP:** Alpha fetoprotein, **ECG:** Electrocardiogram, **MRI:** Magnetic resonance imaging, **MCA:** Middle cranial artery, **LMWH:** Low molecular weight heparin, **LDH:** Lactate dehydrogenase, **APTT:** Activated partial thromboplastin time, **ANA:** Anti-nuclear antibody, **Fib 4:** Fibro test, **APRI:** AST to Platelet Ratio Index, **CKD:** Chronic kidney disease, **SVR:** sustained virological response.

6. CONSENT

Written informed consent for publication of the clinical details was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

7. COMPETING INTERESTS

We have no competing interests.

8. AUTHORS' CONTRIBUTIONS

AZ and MM were responsible for design, acquisition of data, analysis & interpretation of data, writing, literature search, patient management and follow up.

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