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Acute Kidney Injury Associated with Sofosbuvir-Simeprevir in a Patient with Chronic Hepatitis C Virus Infection and HIV Infection: A Case Report

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Abstract Sofosbuvir and Simeprevir are new antiviral agents that have been used to treat chronic hepatitis C virus infection in the recent years with excellent virological response. Both agents are considered to have a safe renal profile. We present a 57-year-old male patient with chronic hepatitis c virus infection who developed acute kidney injury requiring hemodialysis after 7 weeks from beginning of Sofosbuvir and Simeprevir regimen. There was no renal side effects reported in clinical trials of both agents and There was only one reported case of kidney injury in patient taking Sofosbuvir in combination with Ledipasvir.

Keywords: *Sofosbuvir, Simeprevir, Hepatitis C*

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1. Introduction

Sofosbuvir and Simeprevir are new antiviral agents used to treat chronic Hepatitis C virus infection [1], both agents can be used in combination and each one is being used also in combination with other agents [2,3,4,5,6]. Since their introduction in the last few years, both medications have well tolerated safety profiles [1,4,7], there were no reports from clinical trials for both medications of renal side effects [1,8]. There is only one case report of interstitial nephritis that developed after 7 weeks of Sofosbuvir in combination with Ledipasvir (Harvoni) [9], we present another a case report for a patient with a normal kidney function who developed acute kidney injury requiring hemodialysis after initiation of Sofosbuvir and Simeprevir regimen for treatment of his hepatitis C virus infection. We used PubMed portal to search for case reports reporting similar incidences of acute renal failure with the same drugs or their combinations, we limited our search to articles published in English medical literature during the last five years.

2. Case Presentation

Our patient is a 57 year old male patient with a past medical history of paroxysmal atrial fibrillation, hypertension, cerebrovascular accident, chronic Hepatitis C infection and anemia of chronic disease. Our patient has well controlled Human immunodeficiency virus (HIV)) infection maintained on Raltegravir and Emtricitabine/Tenofovir. His other medications are Aspirin, Abciximab, Amlodipine, and Acetaminophen as needed

Our patient was started on Sofosbuvir and Simeprevir to treat his hepatitis C infection, his serum creatinine at time of starting medications was 0.6 mg/dl and GFR was > 60 mL/min/1.73, HCV viral load was 3556853 IU/ml, all other electrolytes and laboratory values were within normal limits except hemoglobin level of 11.5 g/dl with normal mean corpuscular volume (MCV).

Seven weeks after initiation of the therapy he presented to the emergency room with complaints of confusion, altered mental status and shortness of breath, his vital signs at presentation: Blood Pressure: 126/, Pulse: 96, Respiratory rate: 18, O2 sat 97% on 2 L nasal cannula. Lung exam revealed rhonchi bilaterally, cardiovascular examination showed irregular irregular rhythm, there was +2 pitting bilateral lower extremity edema, Neurological exam at presentation: the patient was disoriented to time and not following commands appropriately.

On presentation the Hemoglobin level was 9.7 g/dl white blood cells count was 9.3 X $10^3/mm^3$ with differential 51% neutrophils, his serum chemistry showed sodium level of 136 mEq/L potassium of 4.5 mEq/L chloride level of 98 mEq/L, Bicarbonate level was 27 mEq/L, and an elevated blood urea nitrogen (BUN) was 21 mg/dL and creatinine level was 6.6 mg/dL.

Patient was admitted with diagnosis of acute kidney injury, upon obtaining further history the patient reported history of occasional Ibuprofen intake, he had not undergone any imaging study with contrast prior to the event, there was no identified nephrotoxic agent ingested prior to his illness. At the day of admission patient had Port-A-Cath inserted and started on urgent hemodialysis as the patient had pulmonary edema and uremic symptoms.

The patient then underwent renal biopsy. Light microscopy showed forty three glomeruli, nine of them globally sclerotic. There is diffuse mild to moderate mesangial thickening with increased matrix and some cellularity. There is diffuse acute tubular injury, there is diffuse, mild and focally interstitial inflammatory infiltrate composed of activated macrophages and some eosinophils. Immunofluorescence microscopy reveals no staining for immunoglobulins, complement component. Electron microscopy showed diffuse acute tubular injury with areas of necrosis, glomeruli with increased extracellular matrix, mild to moderate, global glomerulosclerosis, patchy active chronic interstitial inflammation, areas of tubular atrophy with mild interstitial fibrosis and arterio-and arteriolosclerosis.

The patient mental status improved after few dialysis sessions, he was discharged and scheduled for outpatient dialysis. Our patient showed significant clinical improvement, his creatinine level at discharge day was 4.4 mg/dL BUN was 20 mg/dL and CO_2 was 21 mEq/L. Patient was followed up with the nephrologist in the clinic, he continued hemodialysis for 2 months only, his kidney function returned to normal with a new baseline of creatinine 1 mg/dL.

We didn't find any certain events that may contributed to his acute kidney injury, patient list of medications were reviewed , the only medications that was introduced to the patient prior to that event was Sofosbuvir and Simeprevir, although there was no mentioning from manufacturers about any renal side effects, also there is no manufacturer recommendation regarding dosing of these medications in impaired renal function , we decided to discontinue these medications as we suspected they may be the cause of his renal insult given this is the only change in his medications prior to his illness. Another interesting point that the patient has sustained virological response despite he took the medication for only 7 weeks, and during his admission HCV viral load was tested and the viral load was < 15 IU, he has sustained viral response till now.

The patient is following as an outpatient regularly for his chronic HIV infection and he is doing well tell the moment of writing this case report.

3. Discussion

Sofosbuvir *(Sovaldi)* is a nucleotide analog inhibitor of hepatitis C virus NS5B polymerase an enzyme that is essential to HCV RNA replication [10]. Sofosbuvir is indicated for the treatment of many HCV genotypes, in combination with peg interferon, ribavirin or other antiviral agent [4,6]. Sofosbuvir unlike the other antiviral agents is mainly excreted by kidney [10]. Sofosbuvir is also used in combination with Simeprevir for HCV genome type 1 [2]. Simeprevir (*Olysio*) is a NS3/4A hepatitis C virus (HCV) protease inhibitor [11], This is a protein that is responsible for cleaving and processing the HCV-encoded polyprotein, a critical step in HCV life cycle [11]. Simeprevir is mainly excreted by the liver [10].

Since their introduction in the recent years both medications showed good response with few sides effects reported [1,4,7,12,13]. The most serious side effect reported with Sofosbuvir is bradycardia when administered with amiodarone [14].

Treatment with Sofosbuvir-based regimens is associated with a sustained virological response in most patients with chronic hepatitis C virus (HCV) infection reaching 90%, with a very low rate of serious adverse events [15]. Most side effects that has been reported with Sofosbuvir are fatigue, headaches and skin rashes [12].

Simeprevir also has good safety profile and most reported side effects are fatigue, headaches, insomnia and dizziness when taken with Sofosbuvir [13].

Sofosbuvir/Simeprevir regimen was used in our patient as there is evidence of its efficacy and safety [1,4,16], it was commonly used during that period before introduction of one pill combination Sofosbuvir/Ledipasvir *(Harvoni)*.

There was no report in clinical trials about any renal side effects or increase in serum creatinine when taking both agents either together or any one of this medication in combination with other antiviral agent [1,17,18]. Furthermore, there was a study done on patients taking Sofosbuvir and Simeprevir in End stage renal disease on hemodialysis or GFR < 30 mL/min/1.73 m2, and showed that both medications are well tolerated and safe [19].

On other hand there is few studies about Sofosbuvir in patients with low GFR (Less than 45 mL/min/1.73 m2), few percent of the population tested developed worsening kidney function and few patients required hemodialysis initiation [20,21].

There was a case report about a patient with who developed acute kidney injury on top of chronic kidney disease, biopsy proves acute interstitial nephritis, this happened after 7 weeks from initiation of Sofosbuvir in combination with Ledipasvir, however it is unknown which agent cause the problem is it the Sofosbuvir or Ledipasvir or both [9].

Our patient case is unique in aspect that he required hemodialysis therapy despite he has normal kidney function.

Our patient was on Raltegravir/Emtricitabine/Tenofovir/ regimen for HIV infection, patient has been maintained on this regimen for 3 years without adverse events, Tenofovir is known to cause kidney injury in small percent of patients [22,23], However our impression it is unlikely the cause of the renal insult for our patient as he has been taking it for few years , it may possible that an interaction developed between his HIV medications and HCV medication, but there is no reports of any interaction happened when these medications were taken.

4. Conclusion

Physicians should consider monitoring serum creatinine regularly when prescribing Sofosbuvir and Simeprevir for their patients, and should be aware about any interaction that may happen when taking other antiretroviral medications. Clinicians should pay more attention and report any renal side effects that can happen with any new antiviral agents against hepatitis C. The more Data collected for reported side effects can help study the interactions of the medications and therefore side effects can be reduced.

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