Received: 18 April 2021 | Revised: 14 June 2021 | Accepted: 15 June 2021

DOI: 10.1002/ccr3.4539

CASE REPORT

Clinical Case Reports Open Access WILEY

Favipiravir-induced nephrotoxicity in a patient with COVID-19: A case report

Asmaa A. Abdelbary[1] | **Ahmad E. Alharafsheh**[2] | **Afif Ahmed**[3] | **Abdulqadir J. Nashwan**[4]

[1]Pharmacy Department, Home Health Care Services (HHCS), Hamad Medical Corporation, Doha, Qatar

[2]Pharmacy Department, Hazm Mebaireek General Hospital (HMGH), Hamad Medical Corporation (HMC), Doha, Qatar

[3]Corporate Pharmacy Department, Hamad Medical Corporation (HMC), Doha, Qatar

[4]Nursing Department, Hazm Mebaireek General Hospital (HMGH), Hamad Medical Corporation (HMC), Doha, Qatar

Correspondence
Abdulqadir J. Nashwan, Nursing Department, Hazm Mebaireek General Hospital (HMGH), Hamad Medical Corporation (HMC), P.O.Box 3050 Doha, Qatar.
Email: anashwan@hamad.qa

Funding information
This study was not funded

Abstract

This report describes a case of 45 years old male patient who tested positive for COVID-19 presented to the emergency department on March 2021 complaining of fever, cough, runny nose, and shortness of breath. The patient denied any history of nausea or diarrhea who has eventually developed favipiravir-induced nephrotoxicity.

KEYWORDS

acute kidney injury, COVID-19, favipiravir, nephrotoxicity

1 | BACKGROUND

This report describes a case of 45-year-old male patient who tested positive for COVID-19 presented to the emergency department on March 2021 complaining of fever, cough, runny nose, and shortness of breath. The patient denied any history of nausea or diarrhea who has eventually developed favipiravir-induced nephrotoxicity.

COVID-19 (caused by SARS-COV-2) has rapidly spread worldwide through close human interactions or the spilled respirational material (cough and sneeze) of the infected people resulting in a pandemic throughout China, as well as other countries throughout the world.[1]

Acute kidney injury (AKI) is prevalent among patients admitted with SARS-COV-2 infections.[2] Many published studies had addressed this issue as poor clinical outcomes and prognosis accompany it. The mechanism and pathophysiology of renal involvement in SARS-COV-2 infection are unclear. Still, some published literature are justifying it by having COVID-19 related causes such as direct injury to the kidney tissue from the entry of the virus through the receptor angiotensin-converting enzyme ACE2, which is highly expressed in the kidney or non-COVID specific mechanisms like hypovolemia, hemodynamic instability, or sometimes nephrotoxic medications.[3-5]

Favipiravir is an orally administered antiviral nucleotide analog.[6] It inhibits RNA polymerase, which targets both viral shedding and loads with subsequent reduction in mortality and intubation in patients affected with COVID-19.[7] It is one of the primary medications that have been used in the treatment protocol of confirmed COVID-19 mild-to-moderate pneumonia cases in the state of Qatar.

Generally, favipiravir is well tolerated with a good safety profile, and the main reported ADRs are GIT side effects and

elevation in both ALT and AST.[6] Favipiravir did not show a nephrotoxic effect on animal studies. Favipiravir is actively excreted through the renal route, and its serum concentration is expected to increase by twofold to threefold in patients with eGFR of 30–50 ml/min; however, data are lacking and insufficient about the need for renal dosing calculation or adjustment.[8] Clinical trials are excluding patients with severe renal impairment. Favipiravir had shown efficacy in treating COVID-19 pneumonia on some ESRD patients who are maintained on hemodialysis.[9] The drug data basis and monographs are only recommending general caution about worsening renal parameters and kidney functions; however, they lack data about adequate dose adjustments based on current kidney or liver functions.

2 | CASE PRESENTATION

TA is 45-year-old male obese patient (body mass index [BMI] = 35) known case of hypertension (HTN) for more than 10 years controlled on amlodipine 10 mg daily, chronic kidney disease (CKD) with a history of proteinuria (Baseline Srcr 177 mmol/L with calculated Clcr =51 ml/min) Old CVA (Left Basal Ganglia ICH 2016 with right hemiparesis maintained on baclofen 10 mg TID), presented to the emergency department on March 13, 2021 complaining of fever, cough, runny nose, and shortness of breath. The patient denied any history of nausea or diarrhea.

He has positive COVID-19 PCR with an average CT = 29, Temp = 37, a chest X-ray showed mild infiltrates on Lt side blood results on admission are shown on (Table 1).

The patient was started on COVID-19 Medication as per our protocol. favipiravir 1600mg bid received on March 14, 2021 then 600mg bid for total 7 days (received only one day March 15, 2021), ceftriaxone 2gm IV daily for 7 days, and dexamethasone 8mg IV daily for 10 days.

TABLE 1 Laboratory results on admission

Labs	On admission	Reference ranges
Urea	15.1	2.5–7.8 mmol/L
Creatinine	275	62–106 μmol/L
Sodium	133	136–145 mmol/L
Potassium	4.2	3.5–5.3 mmol/L
Chloride	100	95–108 mmol/L
Bicarbonate	17	22–29 mmol/L
Bilirubin T	9	0–21 μmol/L
Total Protein	75	60–80 gm/L
Albumin	32	35–50 gm/L
ALK Phosphatase	67	40–129 μ/L
ALT	23	0–41 μ/L
AST	42	0–40 μ/L
CRP	83.3	0–5 mg/L

We found the patient to have an abrupt elevation on his Src from the baseline admission by 2.7-fold approximately 48 hours after starting favipiravir reaching 489μmol/l with accepted urine output 1.3–1.5 L (see Figure 1); nephrologist was consulted who had ordered for ultrasound kidneys, ureters, and bladder (USG KUB) which showed normal size bilateral kidneys with evidence of chronic parenchymal medical disease as well as autoimmune workup (C3, C4, ANA, anti-GBM) which all came negative to rule out autoimmune kidney disease. Serum creatinine and renal parameters showed trending down after stopping favipiravir until reaching baseline of 169 Mmol/L with adequate renal output also; the patient showed features of resolving respiratory failure; trending down inflammatory markers and successful oxygen weaning off.

The AKI improved within 12–24 hours after favipiravir discontinuation, demonstrating a timely association of favipiravir and the abrupt elevation of renal parameters (nephrotoxicity).

3 | DISCUSSION

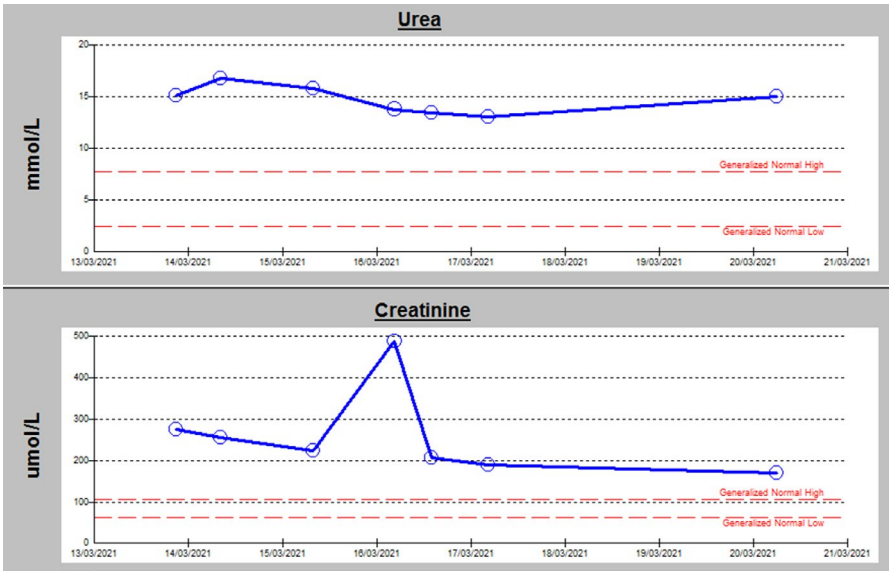
Drug-induced nephrotoxicity is defined by "the presence of any kidney injury caused directly or indirectly by medication".[10] It is common among hospitalized patients, the third main cause of AKI, and anti-infectives had been shown to be one of the most common drug classes associated with it.[11]

Favipiravir had been widely used as an effective antiviral for the management of COVID-19 pneumonia since it was declared as a pandemic last December 2019. Favipiravir had shown better therapeutic responses on COVID-19 pneumonia in terms of disease progression and viral clearance.[12] In another randomized, controlled, open-label multicenter trial, favipiravir was found to significantly improve the latency to relief for pneumonia symptoms like pyrexia and cough.[13]

According to Nasa and colleagues,[14] there was a case report published early this year of two COVID-19 pneumonia male patients (38 and 51 years old) with normal kidney functions at baseline who had developed non-oliguric AKI approximately 48hours after receiving favipiravir on the same dose like that mentioned above. This AKI had improved 24–48 hours after stopping favipiravir and this to a certain extent coincident with the abovementioned findings of our patient apart from that our patient is a known case of CKD.

The presence of CKD was a risk factor of favipiravir-induced nephrotoxicity and AKI in our reported patient case; however in the absence of documented nephrotoxicity in the

FIGURE 1 Urea and creatinine values



drug leaflet and monograph, clinicians may choose to still prescribe the medication in those patients with stable CKD if the anticipated benefit outweighs the highlighted harm and with close monitoring of kidney functions especially that favipiravir had demonstrated an efficacy against COVID-19 patient with ESRD undergoing maintenance hemodialysis.[15]

4 | CONCLUSION

The health care professional need to be very careful of any new adverse events with all the medications used to treat COVID-19 pneumonia as enough evidence from the literature does not support them. The AKI needs a comprehensive review for all possible underlying etiologies and causes before correlating it to COVID-19.

ACKNOWLEDGMENTS

Open Access funding provided by the Qatar National Library.

CONFLICT OF INTEREST

All the authors have declared no competing interest.

AUTHOR CONTRIBUTIONS

AAA, AEA, AAF, and AJN collected data, searched literature, and prepared manuscript. All authors read and approved the final manuscript.

ETHICAL APPROVAL

The article describes a case report. Therefore, no additional permission from our Ethics Committee was required.

CONSENT FOR PUBLICATION

The consent for publication was obtained.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

ORCID

Asmaa A. Abdelbary https://orcid.org/0000-0001-7243-0112
Abdulqadir J. Nashwan https://orcid.org/0000-0003-4845-4119

REFERENCES

1. McIntosh K. Coronavirus disease 2019 (COVID-19): Clinical features. UpToDate Waltham, Mass: UpToDate. 2020.
2. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. 2020;98(1):209-218. http://dx.doi.org/10.1016/j.kint.2020.05.006
3. Hassanein M, Radhakrishnan Y, Sedor J, et al. COVID-19 and the kidney. *Cleve Clin J Med*. 2020;87(10):619-631. http://dx.doi.org/10.3949/ccjm.87a.20072
4. Iqbal F, Soliman A, De Sanctis V, et al. Prevalence, Clinical Manifestations, and Biochemical Data of Hypertensive versus Normotensive Symptomatic Patients with COVID-19: A Comparative Study. *Acta Bio Medica Atenei Parmensis*. 2020;91(4):e2020164. https://mattioli1885journals.com/index.php/actabiomedica/article/view/10540
5. Soliman AT, Prabhakaran Nair A, Al Masalamani MS, et al. Prevalence, clinical manifestations, and biochemical data of type 2 diabetes mellitus versus nondiabetic symptomatic patients with COVID-19: A comparative study. *Acta Bio Medica Atenei Parmensis*. 2020;91(3):1-9. https://www.mattioli1885journals.com/index.php/actabiomedica/article/view/10214
6. Lexicomp. Favipiravir 2021; https://www.uptodate.com/contents/favipiravir-united-states-not-commercially-available-refer-to-prescribing-and-access-restrictions-drug-information. Accessed 29 March 2021.
7. Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. *Int J Infect Dis*. 2021;102:501-508.

8. Marra F, Smolders EJ, El-Sherif O, et al. Recommendations for Dosing of Repurposed COVID-19 Medications in Patients with Renal and Hepatic Impairment. *Drugs R&D*. 2021;21(1):9-27.
9. Koshi E, Saito S, Okazaki M, et al. Efficacy of favipiravir for an end stage renal disease patient on maintenance hemodialysis infected with novel coronavirus disease. *CEN Case Rep*. 2021; 10(1):126-131.
10. Sales GTM, Foresto RD. Drug-induced nephrotoxicity. *Rev Assoc Méd Bras*. 2020;66:s82-s90.
11. Bicalho MD, Soares DB, Botoni FA, Reis AMM, Martins MAP. Drug-induced nephrotoxicity and dose adjustment recommendations: agreement among four drug information sources. *Int J Environ Res Public Health*. 2015;12(9):11227-11240.
12. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering*. 2020;6(10):1192-1198.
13. Chen C, Huang J, Cheng Z, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. *MedRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v4
14. Nasa P, Shrivastava P, Kulkarni A, Vijayan L, Singh A. Favipiravir Induced Nephrotoxicity in Two Patients of COVID-19. *J Assoc Phys India*. 2021;69:88.
15. Koshi E, Saito S, Okazaki M, et al. Efficacy of favipiravir for an end stage renal disease patient on maintenance hemodialysis infected with novel coronavirus disease 2019. *CEN Case Rep*. 2021;10(1):126-131.

How to cite this article: Abdelbary AA, Alharafsheh AE, Ahmed A, Nashwan AJ. Favipiravir-induced nephrotoxicity in a patient with COVID-19: A case report. *Clin Case Rep*. 2021;9:e04539. https://doi.org/10.1002/ccr3.4539