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Case Report

Prudent Use of Favipiravir for COVID-19- A Case Report and Mini-Review of Literature

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Abstract

COVID 19 infection initially termed as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) infection was declared as a pandemic by the World Health Organisation (WHO) on account of its significant morbidity and mortality. The range of presentations of this illness is wide and spans from asymptomatic viral shredding to a mild flu like illness to critical multiorgan involvement and death. The exigent need to curb its transmission lead to the introduction of a purine nucleic acid analog drug named Favipiravir. This drug had already been approved in 2014 by Japan Pharmaceuticals and Medical Devices Agency for the purpose of treatment of influenza A virus infection. Its use in COVID 19 infection is predominantly in mild to moderate cases. However, its oral route of delivery makes it appealing and convenient. Common adverse effect linked with the drug are deranged liver enzymes, increased uric acid level and altered triglyceride levels. As its use in this pandemic is relatively recent, its patient tolerance and profile of its adverse effects is not much elucidated. We, hereby report a moderate SARS CoV-2 case treated with this recently introduced drug Favipiravir who developed acute liver injury secondary to its use.

Keywords: *SARS CoV-2; Purine Analogue; Favipiravir; Liver Enzymes*

Introduction

SARS CoV-2 infection is caused by novel coronavirus-2019 [1], also named COVID-19 by WHO. This infection has affected colossal number of cases globally in a brief duration of time and hence been declared as a pandemic. Manifestations of this disease encompass a spectrum from asymptomatic, influenza like illness (ILI) features in form of cough, fever, sore throat, running nose, myalgia at one end to severe acute respiratory illness (SARI) complicating into Adult Respiratory Distress Syndrome (ARDS) at the other end. Lack of definitive treatment and the nonavailability of a potent vaccine is a major hurdle in battling with this disease. Standard practice of care [2] focuses on symptomatic management along with supportive care. The clinical efficacy of antiviral agents for COVID-19 has not been adequately reported. Till date majorly two antiviral drugs have been shown to have plausible effects in this infection. The first one namely Remdesivir is an intravenous drug which has shown efficacy in moderate to severe cases. The second drug Favipiravir is an oral agent majorly targeted for the mild to moderate cases. It is relatively neoteric and there is not much literature about its field performance and profile. We, hereby report a case of moderate COVID-19 disease treated with this recently introduced drug Favipiravir who developed acute liver injury secondary to its use.

Case Summary

A 30 year old man, with no known comorbidities, presented to us with fever with chills and rigors, dry cough and myalgia of four days duration. He tested positive for COVID-19 on oropharyngeal swab real time polymerase chain reaction (RT-PCR). On admission, patient was hemodynamically stable with oxygen saturation (SPO_2) of 94 - 95% on room air and arterial blood gas (ABG) showed normal study.

His chest roentgenogram (CXR) showed right paracardiac patchy infiltration (Figure 1), high resolution computed tomography (HRCT) showed bilateral ground glass opacity (GGO) with subpleural involvement (Figure 2). On serology, patient had leukocytosis, lymphopenia, raised acute inflammatory markers like c-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH) and borderline raised d-dimer and interleukin-6 (IL-6). His liver enzymes, renal profile, coagulation profile, procalcitonin (PCT) and Troponin-I was within normal limit. He was initiated on Favipiravir 1800 milligram (mg) twice a day (BID) on day 1 followed by 800 mg BID from day 2 onwards along antibiotic (ceftriaxone), low dose steroids, low molecular weight heparin (LMWH), indomethacin, proton pump inhibitor, vitamin supplements and supplemental oxygen. He was monitored with serial liver function tests which showed incremental trend right from day 1. Alanine aminotransferase (AST) was raised upto 10 times upper limit by day 3 without any obvious symptoms, which led us to withdraw Favipiravir. The patient was evaluated with a gastroenterologist evaluation for acute liver injury with ultrasonography abdomen, which showed loss of echotexture of liver. He also had along with borderline elevated international normalise ratio (INR) and Immunoglobulin M (IgM) hepatitis A. He was managed conservatively with Vitamin K for 3 days. His serology normalized with conservative management and withdrawal of the offending drug. His clinical condition also improved with supportive care. Hence, there was no re-introduction of Favipiravir. His RT-PCR oropharyngeal swab converted to negative. Patient was discharged in stable state.

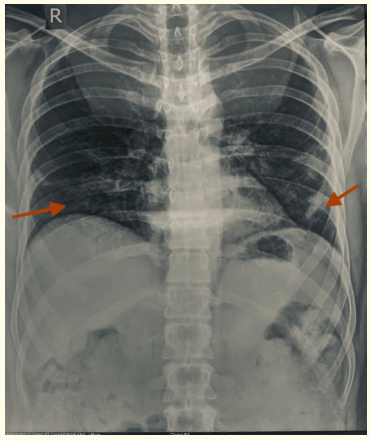

Figure 1: *Chest roentgenogram showing B/L lower zone patchy infiltration.*

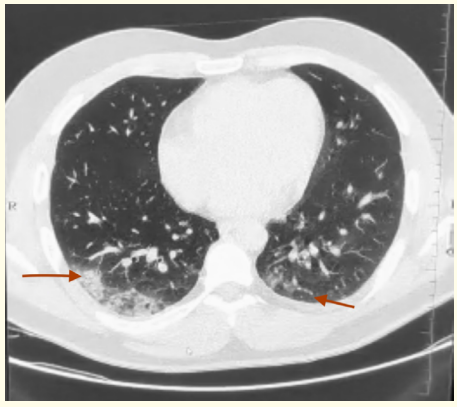

Figure 2: *High resolution computed tomography thorax showing B/L lower zone sub-pleural based ground glass opacities.*

Discussion

The first outbreak of the SARS CoV-2 infection was reported in Wuhan, China in December 2019. On January 30, 2020 India reported it's elemental case and soon the disease was proclaimed as a pandemic by the WHO. The relatively more severely affected population is the elderly, immunocompromised states like malignancy, chronic kidney disease, cardiovascular disease, chronic lung disease and diabetics. SARS CoV-2 is a single stranded ribose nucleic acid (RNA) virus with bilipid layer envelope [3]. The virus spike protein (S-protein) binds with angiotensin converting enzyme-2 (ACE-2) present in the lung, kidney, heart and adipose tissue. The transmission occurs through two principal means namely droplet transmission and fomite transmission. A study from Wuhan reported that the virus is detected for a median period of 20 days (upto 37 days among survivor) after symptom onset, but infectiousness may decline significantly 8 days after the symptom onset. The basic reproduction number (R0) is 1.5 - 4.5 with an average of 2.2 [4]. Pathogenesis [5] of disease can be described as cytokine storm, pneumonia and hypercoagulation leading to endothelial damage, mitochondria dysfunction, micro and macro thrombi, rhabdomyolysis and acute kidney infarction leading to hypovolaemia, shock, acute respiratory distress syndrome (ARDS), myocarditis and multiple organ failure. COVID-19 infection rapidly transits through various stages with some overlap in the stages. These consist of asymptomatic viral shredding (First five days), phase of escalating viremia coupled with onset of symptoms (D5 to D10), phase of cytokine storm (D8 to D14) and convalescent phase (D14 to D28) [6]. Hence, it was exigent to introduce a potent antiviral drug which can decrease the load of RNA concentration in the phase of viremia and can further halt or decrease the intensity of the cytokine storm.

Currently the available armamentarium of antivirals against COVID-19 consists of two drugs namely Remdesivir and Favipiravir. Remdesivir [7] a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown *in vitro* activity against SARS-CoV-2. Drug being costly and more hepatotoxic. These problems with remdesivir are significantly overcome with the recently, introduced Favipiravir. It has shown promising results particularly in mild to moderate cases. Favipiravir is a pyrazine derivative which acts by impeding viral replication by inhibiting RNA dependent RNA polymerase enzyme. Apart from Japan, it has already got approval from countries like China and Italy. The drug is metabolised by cytochrome P-450 (CYP), aldehyde oxidase and partly by xanthine oxidase and excreted as hydroxylated form into urine. In Japanese clinical studies and the global phase III study (lower dose than approved) major untoward effects [8] seen are hyperuricemia (4.79%), diarrhoea (4.79%), neutropenia (1.8%), increase aspartate aminotransferase (AST) (1.80%), increase ALT (1.60%) but these are manageable. Warning has been issued with use in pregnant and family planning persons.

In an open-labelled control study carried out globally [9] Favipiravir showed significant viral clearance time as compared to lopinavir and ritonavir combination. Study also showed early radiology clearing in Favipiravir arm. The safety and tolerability profile was also acceptable. The dose use here was 1600 mg BID on day 1 followed by 600 mg BID for 9 days. Another study [10] which was a prospective, randomised, controlled, open labelled multicentre trial showed promising results with respect to viral clearance, latency to reduce pyrexia and cough as compared to Umifenovir.

In India, a clinical study comparing Favipiravir to standard supportive care in patients with mild to moderate COVID-19 is ongoing. Here, dose is 1800 mg BID on day 1 followed by 800 mg from day 2 onwards maximum upto 14 days. Extra caution needs to be excised if the patient is simultaneously taking pyrazinamide (risk of hyperuricemia) or theophylline (risk of drug toxicity).

Our case showed elevated liver enzymes however on a background of marked clinical improvement right from first dose. This prompted us to continue the culprit drug as various studies have shown that early antiviral administration appears to quickly reduce the viral shedding and decrease the intensity of cytokine storm. However, we were compelled to discontinue the drug with a tenfold increase in the liver enzymes coupled with ultrasonographic evidence of acute liver injury. The treatment available for drug induced acute liver injury [11] is stopping the culprit drug, managing coagulopathy with coagulants like vitamin K and clotting factors and supportive care. Severe cases presenting as hepatic encephalopathy require intensive care unit (ICU) care, intubation for airway protection, nasogastric tube placement, dietary supplement with branched chain amino-acid, lactulose, rifaximin, l-ornithine and l-aspartate (LOLA), n-acetyl cysteine and frequent bowel wash.

Conclusion

Introduction of Favipiravir seems to be a ray of hope in midst of despair in the treatment COVID-19 by the virtue of its ease of administration, cost effectiveness and efficacy in mild to moderate cases. However, it needs to be used cautiously in alcoholics, pregnancy and individuals with preexisting liver disease. Also, a close monitoring with clinical examination and liver enzymes is vital for timely diagnosis of acute liver injury and opportune discontinuation of the drug.

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Conflict of Interest

Nil.

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