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Research Article,

Remdesivir and Favipiravir Changes Hepato-Renal Profile in COVID-19 Patients: A Cross Sectional Observation in Bangladesh

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Abstract:

Coronavirus disease (COVID-19) is the current global public health concern. To date, no specific, effective, and approved treatment is available. With the rapid increase in the rate of infection, repurposing the use of anti-viral like remdesivir and favipiravir was considered as an option to find promising anti-COVID therapeutics. In this study, we aim to observe hepato-renal safety concerns related to these drugs. This retrospective study was done from May 17 to September 9, 2020, on a total of 1348 hospital records. 182 patients were included in the study, divided into two groups who received remdesivir only (RO) and favipiravir only (FO). The mean age of the respective groups is 59.42 (RO) and 54.64 (FO). The average duration of hospital stay was 11 to 12 days. The mortality rate (28.39%) was higher in the RO group. Mean± SD of both ALT (70.65± 50.25) and AST (62.25± 25.46) levels was increased in the RO group than FO group. On the other hand, Blood urea (56.67± 38.40) and serum creatinine (01.70± 02.41) level was higher in the FO group. Hematuria was absent in both groups, proteinuria was also unremarkable. In patients with Covid-19 receive remdesivir and favipiravir, showed an elevation in the level of hepato-renal markers.

Keywords: COVID-19. Remdesivir, Favipiravir, ALT, AST, Serum creatinine

Interoduction:

COVID- 19 has infected around 45 million people and claimed over 1.1 million deaths in 213 countries and territories around the world[1]. This huge number of infected patients with a global mortality rate of 4.3% to 11% demonstrates that the coronavirus disease is extremely contagious. On 11 March 2020, WHO announced COVID-19, a global pandemic? Near the time of this announcement, the first case of Severe Acute Respiratory Syndrome Corona Virus – 2 (SARS – COV – 2) was reported in Bangladesh on 8th March 2020. From then to October 30th, 2020, 4, 04, 760 confirmed cases and 5,886 deaths were reported in Bangladesh[2]. Besides Bangladesh, COVID heat the densely populated South Asian region with 8,395, 617 confirmed cases and 1, 28, 625 deaths up to October 19, 2020[3]. Government of this region, taken various measures to contain the COVID-19 spread, such as nationwide lockdown, quarantine curfews, restrictions on travel, mass gatherings, the practice of personal hygiene, and social distancing. This pandemic situation has a significant impact on this densely populated region, not only the health sector but also economy[3]. People with COVID-19 symptoms are quarantined at home and treated in COVID dedicated hospitals. The clinical characteristics of COVID-19 include fever, headache, dry cough, diarrhea, weakness, sore throat, nasal congestion, and shortness to breathe. In the case of 80% of patients, SARS-COV-2 infections are self-limiting and special treatment may not require,15% of the infected patients may present with co-morbidities such as diabetes mellitus, ischemic heart disease, hypertension, and obesity are more likely to develop severe pneumonia, admitted to the emergency department of health facilities to get proper care and rest 5% progress to respiratory failure, acute respiratory distress syndrome (ARDS) and need intensive care unit (ICU) support for a long period of time[4]. No specific treatment exists for COVID-19 yet. The standard practice of care focuses on treating the clinical

symptoms (pyrexia, cough), and acute respiratory distress syndromes (ARDS) of patients with supportive care such as fluid management and auxiliary oxygen therapy. The clinical efficacy of antiviral agents for COVID-19 is, so far not approved[5,6].

To develop, evaluate, and obtain approval for a new potent anti-COVID-19 agent could take more than ten years. In the present scenario, the development of a new therapeutic agent for COVID-19 is not a better option regarding the urgency of the situation. Therefore, re-purposeful use of existing anti-virals can be a feasible option due to their availability, known pharmacokinetics, pharmacodynamics property, and adverse effects. Several drugs, such as ribavirin, interferon, favipiravir, remdesivir, and lopinavir/ritonavir, have been used in COVID patients, although the efficacy of some drugs yet to be approved[7]. Among them, remdesivir and favipiravir are included in the national guideline of Bangladesh. Remdesivir is previously tested against Ebola virus disease[8]. Remdesivir (RDV) is a broad-spectrum antiviral drug block viral nucleotide synthesis to stop viral replication of sarscov[9]. In a recent cohort study, the patient admitted to ICU, treated with RDV for 10 days, clinical improvement was observed in 68% of patients[10]. Another RCT in Hubei reported that RDV use did not show a significant association between differences in time to clinical improvement. Adverse events were reported in 66% of RDV recipients versus 64% in placebo recipients[11].

Favipiravir is a purine analog that acts as an alternate substrate. This substrate is responsible for inaccurate viral RNA synthesis[12]. In a recent RCT in china which included adult patients with COVID-19 showed no significant difference in Favipiravir group in the term of clinical recovery rate. The most frequently reported adverse event was increased serum uric acid level in the favipiravir arm which were mild and manageable[13]. In the DHAKA trial. 50 COVID-19 positive patients treated with favipiravir showed a negative result in 48% after four days of treatment and by the tenth day, that number came to 96%[14].

The most common unwanted effects of antiviral drugs include gastrointestinal problems, blood disorders, and CNS effects, and hypersensitivity reactions[7]. In a matter of safety profile, abnormal liver function is common in the case of remdesivir as increases liver enzyme level may be a sign of inflammation or damage to cells in the liver[15]. This drug also can lead to mitochondrial injury in renal tubular epithelial cells. So, its use is limited in patients with kidney disease. Treatment with antiviral for patients with COVID-19 having acute kidney injury and end-stage kidney disease has a high risk of excess morbidity and mortality[16]. Favipiravir, predominantly excreted through the urine, causes a change in the liver and renal function test[7]. Therefore, remdesivir and favipiravir are considered as the potential candidates for COVID-19, although confirmed in vitro and preclinical animal studies are not available yet. Safety analysis is important for limiting widespread use. Therefore, a retrospective study, regarding the hepato- renal safety of both drugs in admitted COVID-19 patients was conducted.

Method:

The retrospective single center study was done in Holy Family Red Crescent Medical College Hospital, a COVID-19 dedicated 720-bed tertiary care hospital in Dhaka, Bangladesh, from May 17 2020 to September 9 2020. The study was approved by the hospital authority and the institutional ethics board (IERB/28/Res/Jul/2020/22/hf). Total of 1348 patients included in this retrospective study were confirmed as COVID-19 by RT- PCR. Hospital files of all admitted patients were screened. 182 Patients who were treated with remdesivir or favipiravir only and during their hospital stay were included in this study. Patients who have received other antiviral drugs like tocilizumab or bacterinub and had a history of both remdesivir and favipiravir administration was excluded from the study. Most of the patients also received a broad-spectrum antibiotic, low molecular weight heparin, antihistamine, immunity booster like vitamin D, vitamin C, and zinc along with both antivirals. Patients were divided into two groups; receiving (i) remdesivir only (RO) has 81 patients (ii) favipiravir only (FO) has 101 patients. Demographic data along with symptoms, co-morbidities, hospital stay, and mortalities were recorded. Then hepatic markers ALT, AST, APTT, prothrombin time, and INR were recorded in a customized data collection sheet. Renal markers like blood urea, serum creatinine, proteinuria, and hematuria were also recorded.

Result:

Table 1: Demographic data of COVID patients who received remdesivir and favipiravir (n= 182)

Characteristics	RO (n= 81)	FO (n= 101)
Age (year) — mean± SD	59.42± 14.99	54.64± 12.38
0-19 — no./total no.(%)	0/81 (0%)	0/101 (0%)
20-39	05/81 (6.17%)	16/101 (15.84%)
40-59	34/81 (41.97%)	50/101 (49.5%)
60 and above	42/81 (51.85%)	35/101 (34.65%)
Gender — Male/ Female	57/24	60/41
Comorbidities — no./total no. (%)		
DM	48/81 (59.26%)	45/101 (44.55%)
HTN	39/81 (48.15%)	47/101 (46.53%)
Bronchial asthma	02/81 (2.47%)	09/101 (08.91%)
CKD	04/81 (04.94%)	11/101 (10.89%)
IHD	13/81 (16.05%)	18/100 (17.82%)
Thyroid disease	04/81 (04.94%)	05/101 (04.95%)
Cancer	03/81 (03.70%)	00/101 (0%)
Symptoms — no./total no. (%)		
Fever	36/ 81 (44.44%)	50/101 (49.50%)
Cough	26/ 81 (32.09%)	48/101 (47.52%)
Diarrhea	02/ 81 (02.47%)	14/101 (13.86%)
Lethargy	12/81 (14.81%)	16/ 101 (15.84%)
Breathlessness	70/ 81 (86.42%)	64/101 (63.37%)
Myalgia	06/81 (07.41%)	09/101 (08.91%)
Anosmia	00/81 (0%)	04/101 (03.96%)
Sore throat	02/ 81 (02.47%)	04/101 (03.96%)
Loss of taste	02/ 81 (02.47%)	07/101 (06.93%)
Hospital stay (days) — mean± SD	11.01± 8.65	12.39± 08.01
Mortality — no./total no. (%)	23/ 81 (28.39%)	05/101 (04.95%)

Data are presented as mean± SD or as number and percentage. RO= Remdesivir only, FO= Fevipiravir only.

A total of 117(64.28%) patients were men, 51.85% patients were 60 years and above in RO group. 49.5% in FO. A higher prevalence of co morbidities including Diabetic Mellitus, Hypertension, chronic kidney disease and Ischemic heart disease in both groups. Hospital stay around 11 to 12 days in both group. Mortality rate was higher in RO group (Table 1).

Besides antiviral, all patients received acetaminophen, low molecular weight heparin, anti- histamine, vitamin C, D, E and zinc routinely.

Table 2: Changes in liver function test

Markers — mean± SD	RO (n= 81)	FO (n= 101)	*t*-test
ALT (IU/liter)	70.65± 50.25	61.96± 47.15	*p*=0.407345 not significant
AST (IU/liter)	62.25± 25.46	54.67± 34.10	
APTT (Sec)	46.23± 10.99	41.62± 09.68	
Prothrombin time (Sec)	14.83± 04.01	14.28± 02.54	
INR	01.22 ± 0.99	01.08± 0.23	

ALT (70.65± 50.25) and AST (62.25± 25.46), APTT (46.23± 10.99), prothrombin time (14.83± 04.01) and INR (01.22 ± 0.99) were higher in RO group but statistically not significant (Table 2).

Table 3: Changes in renal function test

Markers — mean± SD	RO (n= 81)	FO (n= 101)	*t*-test
Blood urea	30.07± 34.02	56.67± 38.40	*P*=0.353264 not significant
Serum creatinine	01.38± 01.53	01.70± 02.41	
Proteinuria — no./total no. (%)			
Negative	17/ 45 (37.77%)	40/80 (50%)	
Trace	05/ 45 (11.11%)	07/80 (08.75%)	
1+	16/ 45 (35.55%)	21/80 (26.25%)	
2+ to 3+	07/ 45 (15.55%)	12/80 (15%)	

Level of serum creatinine (01.70± 02.41) and blood urea

(56.67± 38.40) level was high in FO group than RO group but statistically not significant. Routine urine examination of 125 patient revealed only (15%) has severe proteinuria and none of the patient had hematuria (Table 3)

Discussion:

Antiviral drugs are used re-purposefully and compassionately during COVID. It needs a decade to develop and approve a potent anti- COVID agent. In the present scenario, remdesivir and favipiravir give the ray of light of hope. In demographic data, most of the patients were men, above 60% of the total population. 75% and 56% of men also showed in other study[10,11]. The majority of the patients who receive remdesivir were 60 and above like other study[9]. Favipiravir mostly received by the middle-aged group. Comorbidities like hypertension, diabetic Mellitus, ischemic heart disease, chronic kidney disease were observed. Researchers also found these comorbidities around the world in COVID-19 patients[10,11]. Most of the patients present with fever, cough, shortness of breath, and lethargy like other study[12]. Guan et al conduct a large cohort including 1099 patients from 552 hospitals in 31 provinces or provincial municipalities, Elevated levels of ALT were observed in 120 (19.8%) of patients with the non-severe disease and 38 (28.1%) of 135 patients with severe disease[16]. Holshue et al reported an elevated level of ALT in their patient in the united states[17]. Increased ALT level from the normal value in RO and FO group was observed which were not statistically significant.

Elevated levels of AST were observed in 112 (18.2%) of 615 patients with the non-severe disease and 56 (39.4%) of 142 patients with severe disease[18]. In a study in The Lancet by Huang and colleagues, the elevation of AST was observed in eight (62%) of 13 patients in the intensive care unit (ICU) compared with seven (25%) of 28 patients who did not require care in the ICU. 43 (53.1%) COVID patients have abnormal liver function[19]. Transient elevations in liver enzymes have been observed after treatment with remdesivir among healthy volunteers[20]. In an RCT on remdesivir, 2.5% and 3.6% of patients in the 5-day and 10-day groups, respectively, discontinued treatment owing to AST elevations[21]. Feng G et al, show in their reviews, in highly epidemic areas of COVID-19 infection, have the proportion of infected patients with elevated serum AST levels is greater than that observed in regions where a smaller proportion of cases of COVID-19 infection in the population have occurred. The proportion of infected patients with elevated AST levels is higher in adults than in children and men than in women[22]. An increase AST level was also observed in RO and FO groups which were not statistically significant.

Huang et al found the incidence of acute kidney injury was 7%, and 3 out of 13 (23%) patients in the intensive care unit[19]. In another study of 99 patients with COVID-19, seven cases developed various degrees of kidney injury with elevated serum creatinine[23]. Wang et al reported that 3.6% of patients developed acute kidney injury in his 138-patient cohort study[6]. In a larger multicenter study with 1,099 cases, Guan et al showed that the acute kidney injury incidence rate was only 0.5%[16]. However, in a single-center study with 710 consecutive hospitalized COVID-19 patients, Cheng et al. reported that patients with elevated baseline Serum creatinine levels have a higher death rate[23]. Another trial reported elevations in serum creatinine level after remdesivir administration[20]. Patients with COVID-19 may have various degrees of renal dysfunction, characterized by elevation of serum creatinine, and renal structural changes[22]. Elevated level serum creatinine in all three RO, FO, RF groups were observed in this study which was not statistically significant.

A study of 59 patients with COVID-19 found that 34% of patients developed massive albuminuria on the first day of admission and 63% of patients presented proteinuria during their stay in hospital[24]. Cheng et al. recently reported that 44% of patients presented with proteinuria and hematuria and 26.9% had hematuria on admission among 710 consecutive hospitalized patients with COVID-19, and the prevalence of elevated serum creatinine was 15.5%[23]. Hematuria was absent and proteinuria was negative in a higher percentage in both groups were observed.

Conclusion:

Remdesivir and favipiravir are so far considered as one of the potential antivirals in treating COVID-19 patients. The present study revealed that the renal biomarkers were high in the favipiravir treated patients, whereas the hepatic markers in remdesivir treated patients. Though the changes were not statistically significant, a further multi-centric study on a larger sample size may provide a clearer picture of the hepato-renal effect of those drugs widely used in the pandemic.

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