International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2023.585.594

Research Article
Safety Analysis of Antiviral Drugs Approved for COVID-19 in Saudi Arabia

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Abstract

Background and Objective: The Coronavirus Disease 2019 (COVID-19) continues to spread in several regions worldwide. Some antiviral drugs have been approved for clinical indication but are associated with several unwanted effects. The present study analyzed four antivirals, namely, remdesivir (Remd), molnupiravir (Moln), ritonavir (Rito) and nirmatrelvir (Nirm), which have been approved for COVID-19 in Saudi Arabia for incidences of adverse effects. **Materials and Methods:** Safety information of these agents was retrieved from electronic databases such as PubMed, SCOPUS, Web of Science and BIOSIS by using the keywords COVID-19, antivirals, safety, side effects and human trials as per the procedures described in the literature. The study analyzed eighteen articles and their data was statistically evaluated, including logistic regression analysis for incidences of side effects categorized under important human body systems. **Results:** Data analysis indicated that Remd significantly ($p<0.05$) increased the incidences of anxiety, apnea, alanine transaminase elevation, hepatitis, diarrhea and hypersensitivity compared to placebo. While Moln increased ($p< 0.05$) the frequency of apnea, oliguria, constipation and hypersensitivity. Rito was associated with anemia, headache and Nirm-enhanced hypertension, diarrhea and hypersensitivity. The correlation analysis indicated that the odd ratio for Remd (OR = 0.41, P = 0.039, 95% CI = 0.106/0.086) and Moln (OR = 0.31, P = 0.045, 96% CI = 0.18/0.077) was significantly varied compared with placebo. **Conclusion:** The observation from the study indicated that the administration of Remd was mild-moderately correlated with the side effects, while Moln is mildly and Rito and Nirm weakly associated with side effects. Although the incidences of serious adverse events were found to be enhanced with Remd the treatment also reduced the mortality rate. Further, the long-term effects of these antivirals need regular updates.

Key words: COVID-19, Saudi Arabia, remdesivir, molnupiravir:ritonavir, nirmatrelvir, safety analysis, healthcare

Citation: Asdaq, S.M.B., M.M. Almutairi, M.S. Alharbi, F.G. Alharbi and A.A. Alharbi *et al*., 2023. Safety analysis of antiviral drugs approved for COVID-19 in Saudi Arabia. Int. J. Pharmacol., 19: 585-594.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is caused by a new strain called Severe Acute Respiratory Syndrome (SARS) coronavirus-2[1]. The virus is a single-stranded RNA belonging to the genus *Betacoronavirus* and its genome presents similarities with SARS coronavirus (≈79%) and Middle East Respiratory Syndrome coronavirus (≈50%)[2]. In December 2019, the virus was first identified in Wuhan city of China and soon attained a pandemic state infecting millions of people worldwide[1].

The COVID-19 generally produces mild clinical manifestations such as fever, chills, cough, body pain, headache and fatigue, resembling the seasonal flu. However, few, especially the old and comorbid patients, cause severe pneumonia, shortness of breath, multi-organ failure and even death[3]. The first case of COVID-19 in Saudi Arabia was detected in March 2020 and soon the infection spread throughout the country[4]. In compliance with the World Health Organization (WHO) guidelines, the healthcare authorities took several proactive measures to curb the spread of infection. Treatment of the infected patients was also strictly followed as per the international standards and norms of WHO[5].

Like other RNA viruses, coronavirus-2 also represents characteristic steps during replication, such as adsorption, penetration, uncoating, nucleic acid synthesis, protein synthesis, packaging and release[6]. The researchers targeted these steps of replication to treat COVID-19 in patients. Several medications were being tested on a trial basis to control the spread of infection or treat the symptoms in patients[7]. These medications in early trials were found to be efficacious but, when tested in multi-centers, were reported to exhibit non-significant action on COVID-19[8].

Some drugs tested early for COVID-19 include chloroquine, hydroxychloroquine, oseltamivir, remdesivir, lopinavir and ritonavir[9]. The efficacy of these medications reported from different regions has conflicting data. Some countries, therefore, recommended these agents for managing mild to moderate cases of coronavirus infection[10]. However, recent studies suggested that these agents lack efficacy against coronavirus and induce unnecessary adverse reactions in patients[11]. Accordingly, WHO regularly updated the list of drugs for COVID-19 by either adding new therapeutic interventions or deleting the existing agents. Furthermore, WHO indicated a statutory warning highlighting the adverse reactions associated with these medications[12], lack of efficacy, unexpected complications of COVID-19 medications and spread of infection has created a sense of insecurity and apprehension among the general public and healthcare providers[13].

The available evidence from the literature indicated that the WHO recommended antiviral agents as emergency use authorization[14]. Some of these agents, such as remdesivir, molnupiravir, ritonavir and nirmatrelvir have been listed among the approved drugs for COVID-19 in Saudi Arabia[15]. These medications inhibit the replication process of coronavirus-2 at different stages. However, administrations of these drugs were reported to cause complications such that remdesivir caused hypersensitivity, chest tightness and mouth and tongue swelling in some patients[3,10]. Molnupiravir was also found to produce similar side effects as remdesivir. Ritonavir causes diarrhea, heartburn, headache, numbness of feet and muscle pain. And nirmatrelvir produces blistering of the skin, nausea, vomiting and irritation of the eyes[14,16].

Summarizing the important and most frequently observed side effects could provide comprehensive data on the possible unwanted effects expected with the antiviral drugs for COVID-19[17]. This information might be helpful for both healthcare providers and the public in adding knowledge about antiviral drugs and might clarify the safety apprehensions about the therapy[18]. The study also assumes importance since the research has yet to identify a specific and safe therapeutic intervention for treating COVID-19[3,10,14]. Hence, this work analyzed the common side effects according to important systems and examined their likelihood of administering antiviral drugs approved in Saudi Arabia.

MATERIALS AND METHODS

Study design: According to the approved drugs by the Ministry of Health, Kingdom of Saudi Arabia, the list of antiviral agents for COVID-19 includes remdesivir (100 mg), molnupiravir (800 mg), ritonavir (100 mg) and nirmatrelvir (150 mg)[14,19]. The safety analysis of these compounds was conducted as per the studies reported in the literature[14-17].

Strategy for retrieving the information from literature: From January, 2021 to March, 2023, keywords like COVID-19 medications or Coronavirus Disease 2019 antivirals or COVID-19 drugs and Safety Profile or Adverse effects and Human Trials or Clinical Studies and Approved were used in an electronic literature search of PubMed, SCOPUS, Web of Science and BIOSIS.

Research plan: The literature search results for four COVID-19 medications, including remdesivir, molnupiravir, ritonavir and nirmatrelvir, which have been licensed in Saudi Arabia, were independently evaluated by the authors participating in this study[15]. The eligibility screening for choosing the published articles was carried out in two steps: The first stage involved

screening the retrieved records' titles and abstracts and the second involved screening the full-text versions of the abstracts that were chosen in the first phase. Any differences in the findings were discussed with the subject matter experts in order to be resolved.

Eligibility criteria: Studies meeting the following requirements were reviewed:

- English-language articles include comprehensive details on the kind of COVID-19 medications used as well as the quantity of willing volunteers
- Published cross-sectional research in the last two years (2021-2023)
- Studies in which COVID-19 antiviral testing was done on human participants
- Studies assessed the COVID-19 antivirals' safety, taking into account dosage, duration, adverse responses and protocols for clearly documenting unforeseen occurrences
- Publications that provide in-depth information regarding statistics and their importance have been published in reputable journals

Studies that didn't fit the qualifying requirements listed above were disqualified. research with duplicate reports, overlapping data sets and research with unextractable data were also excluded[1,20].

Extraction of required data from the research article: The data was separately obtained by the authors using a pre-planned data extraction sheet. The data that was taken from the study included information on the population's makeup, the study's design and its results. English language, study center, subject count, research design, study protocol, dose, duration, mode of administration, ethical permission, statistical techniques and biochemical calculations were among the details that were deemed to be important factors for content evaluation[21]. Important systems such as the cardiovascular, blood, neurological, respiratory, hepatic, renal, gastrointestinal, metabolic and immune systems were the ones with the highest negative effects associated with antivirals[22].

Assessing the quality of the retrieved articles: The Newcastle-Ottawa scale was employed to assess the risk of bias in cross-sectional research. The sample design, statistical analysis description and results[23] are three crucial aspects of this instrument. The quality of the included studies was evaluated by the authors in a blinded manner and any discrepancies were resolved by discussion with the supervisor or topic expert. There were almost 1,500 items found in the literature search. However, based on the inclusion criteria, only 18 publications were chosen for the current study. These articles were submitted for analysis as detailed in the section below after scoring higher than 3 on the Newcastle-Ottawa scale.

Statistical analysis: An Excel spreadsheet was used to capture the information that was taken from the articles. The variables' mean and standard deviation were used to represent them. The IBM SPSS 21.0 software was used to statistically analyze the data. The data were processed and a non-parametric *post hoc* Test was used to determine the statistical significance of the results across groups[21,22]. The Mann-Whitney's U Test for variables and the Chi-square Test for correlation analysis were utilized in the study, both of which were recorded in the sample population following various antiviral therapies. When comparing the studied data, significance was denoted by a $p<0.05$.

RESULTS

The demographic characteristics of the participants were represented in Fig. 1. The percentage of males who participated in the studies was 48.6% in placebo, 59.6% in Remd, 47.7% in Moln, 60.2% in Rito and 55.1% in Nirm, and correspondingly, the female participation was, 51.4 in placebo, 40.4% in Remd, 52.3% in Moln, 39.8% in Rito and 44.9% in Nirm. The age-wise distribution was categorized into 18-40 years, 41-60 years and above 60 years. In placebo, the highest percentage of participants were aged above 60 years (35.2%), while 41-60 years were found to be in Remd (42.4%), Moln (38.6%), Nirm (39.2%) and in Rito, it was 18-40 years (41.7%).

Analysis of cardiovascular and blood system side effects was represented in Table 1. The most frequent cardiovascular side effects observed were dysrhythmia and hypertension. Comparison of data between placebo and different antiviral tested drugs indicated a non-significant variation in both the incidences of dysrhythmias. However, Nirm treatment increased blood pressure significantly ($p<0.05$) compared to placebo and the percentage increase was 15.5%. On the other hand, in two common side effects of the blood system, such as anemia and thrombosis, the data analysis suggested that Rito treatment increased significantly ($p<0.05$) the frequency of anemia compared with the placebo. The percentage likelihood of anemia after Rito treatment was found to be 7.5% in comparison with placebo. Other treatments did not show significant variations in the incidences of anemia and thrombosis compared with placebo.

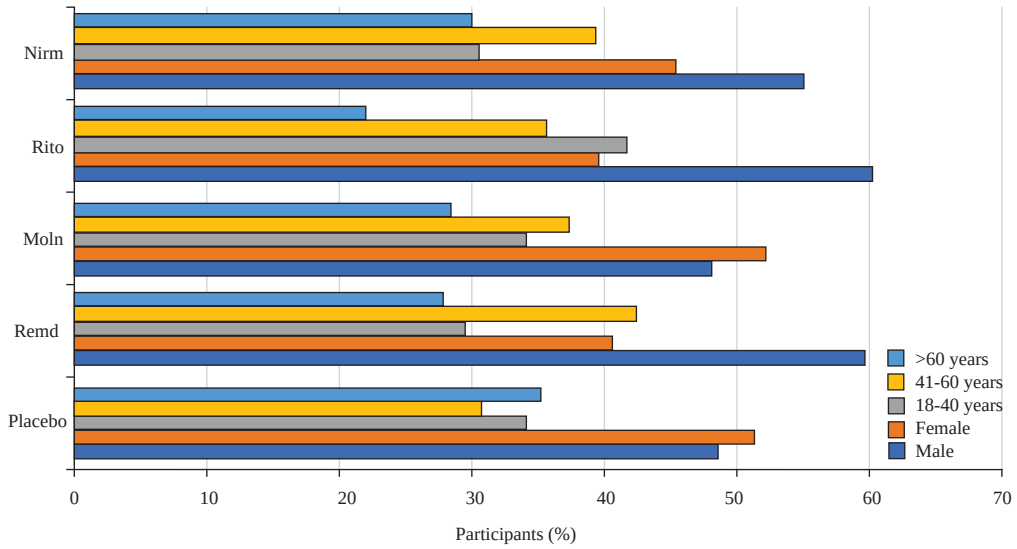

Fig. 1: Percentage of participants who took part in the analysis of side effects after antiviral drug treatment
Remd: Remdesivir, Moln: Molnupiravir, Rito: Ritonavir and Nirm: Nirmatrelvir

Table 1: Common cardiovascular and blood system side effects observed after antiviral drugs treatment

	Cardiovascular system		Blood system	
Treatment	Dysrhythmia	Hypertension	Anaemia	Thrombosis
Placebo	0.42±0.01	0.71±0.11	0.66±0.02	0.59±0.09
Remd	0.44±0.07	0.70±0.17	0.69±0.14	0.58±0.04
Moln	0.40±0.05	0.72±0.08	0.61±0.11	0.61±0.12
Rito	0.43±0.08	0.68±0.14	0.71±0.12*	0.59±0.07
Nirm	0.41±0.09	0.82±0.22*	0.68±0.11	0.63±0.14

Remd: Remdesivir, Moln: Molnupiravir, Rito: Ritonavir and Nirm: Nirmatrelvir, values are represented as Mean±SD, Statistics: One-way ANOVA followed by Mann-Whitney U Test and *p<0.05 compared with placebo

The incidences of anxiety and headache under the nervous system were analyzed and the data indicated that Remd treatment significantly ($p<0.05$) increased anxiety. In contrast, Rito increased significantly ($p< 0.05$) the headache in the tested participants when compared with placebo. The percentage increase for the incidence of anxiety with Remd was 18.4 and for headache with Rito was 10.8%, compared with the placebo data.

The respiratory system side effects, such as apnea and bronchospasm after treatment with different antivirals, were compared with placebo. The analysis suggested that Remd and Moln significantly ($p<0.05$) increased apnea. The percentage occurrences of these side effects were 11.5% with Remd (apnea) and 12.5% with Moln (apnea) upon comparison with placebo. None of the treatments significantly increased the frequency of bronchospasms (Table 2).

Table 3 represented the hepatic and renal system side effects observed with antiviral drugs. Significant incidences ($p<0.05$) of ALT elevations and hepatitis were observed with Remd compared to placebo. The percentage increase in ALT levels and hepatitis was found to be 13.8 and 27.6%, respectively, compared with placebo. In the renal system, acute kidney injury was not significantly altered after different antiviral treatments compared with a placebo. Further, oliguria was found to be increased significantly ($p<0.05$) with Moln when the data was compared with placebo. The percentage increase in the frequency of oliguria with Moln was 7.95% compared to placebo.

The gastrointestinal, metabolic and immunological side effects observed after antiviral treatment were summarized in Table 4. Diarrhea and constipation were the most frequently observed side effects in the gastrointestinal system. Analysis of data suggested that Remd and Nirm significantly ($p<0.05$) increased the incidences of diarrhea, while Moln increased significantly ($p<0.05$) constipation in comparison with placebo. The percentage increase in these side effects after the administration of Remd, Nirm, Moln and Rito was found to be 22.8, 43.22, 9.32 and 11.1%, respectively.

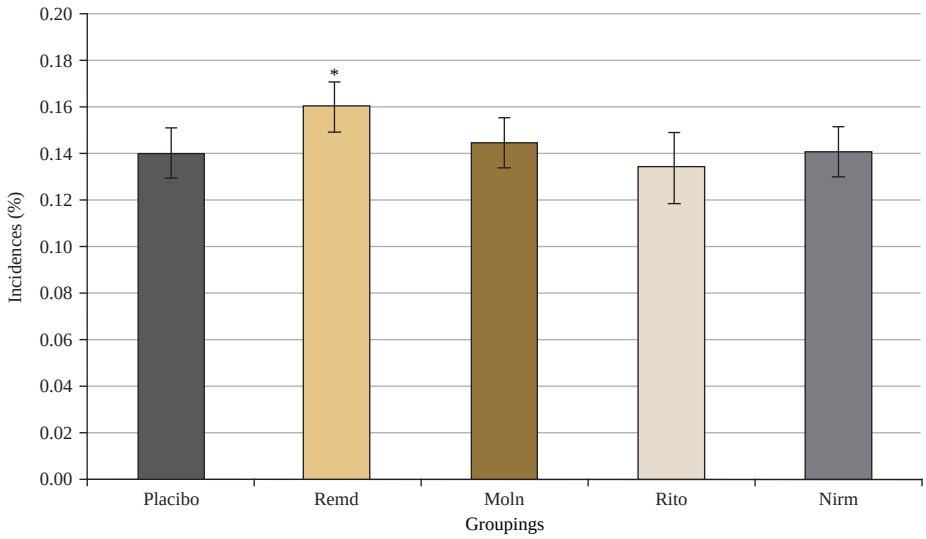

Fig. 2: Percentage of incidences of serious adverse events observed with different antiviral treatments

Remd: Remdesivir, Moln: Molnupiravir, Rito: Ritonavir, Nirm: Nirmatrelvir, values are represented as Mean±SD, Statistics: One-way ANOVA followed by Mann-Whitney U Test and *p<0.05 compared with placebo

Table 2: Common nervous and respiratory system side effects observed after antiviral drugs treatment

	Nervous system		Respiratory system	
Treatment	Anxiety	Headache	Apnea	Bronchospasm
Placebo	0.98±0.12	1.76±0.29	1.04±0.07	0.72±0.03
Remd	1.16±0.35*	1.44±0.12	1.16±0.26*	0.71±0.21
Moln	1.01±0.18	1.80±0.41	1.17±0.28*	0.73±0.21
Rito	0.91±0.24	1.95±0.39*	0.95±0.33	0.70±0.11
Nirm	0.88±0.17	1.68±0.31	1.03±0.24	0.71±0.26

Remd: Remdesivir, Moln: Molnupiravir, Rito: Ritonavir and Nirm: Nirmatrelvir, values are represented as Mean±SD. Statistics: One-way ANOVA followed by Mann-Whitney U Test and *p<0.05 compared with placebo

Table 3: Common hepatic and renal system side effects observed after antiviral drugs treatment

	Hepatic system				Renal system			
Treatment	ALT elevation	#Change (%)	Hepatitis	#Change (%)	Acute kidney injury	#Change (%)	Oliguria	#Change (%)
Placebo	0.36±0.02		0.29±0.14		0.28±0.04		0.81±0.10	
Remd	0.41±0.11*	13.8	0.37±0.11*	27.6	0.26±0.03	-7.35	0.66±0.07	-22.72
Moln	0.38±0.17	7.89	0.28±0.21	-3.45	0.26±0.02	-7.35	0.88±0.11*	7.95
Rito	0.34±0.09	-5.66	0.31±0.08	6.89	0.29±0.04	-3.45	0.82±0.19	1.12
Nirm	0.37±0.10	2.77	0.29±0.23	0.00	0.30±0.08	6.77	0.79±0.12	-2.47

ALT: Alanine transaminase, Remd: Remdesivir, Moln: Molnupiravir, Rito: Ritonavir and Nirm: Nirmatrelvir, values are represented as Mean±SD. Statistics: One-way ANOVA followed by Mann-Whitney U Test, *p<0.05 compared with placebo and #Percentage change when compared to placebo

The major side effect recorded for metabolism and immunology was hyperglycemia and hypersensitivity. The data analysis for hyperglycemia suggested that none of the antiviral treatments significantly altered the blood glucose level compared with the placebo. And, on the incidences of hypersensitivity, Remd, Moln and Nirm were found to significantly ($p<0.05$) enhance the allergic reactions compared with the placebo group. The percentage increase in these reactions with Remd, Moln and Nirm was observed to be 29.7, 25.9 and 20.6%, respectively.

The percentage incidences of serious adverse events with placebo, Remd, Moln, Rito and Nirm were found to be 0.14, 0.16, 0.144, 0.134 and 0.14%, respectively. Among them, the analysis suggested that only Remd administration significantly ($p<0.05$) enhanced the serious adverse events compared to placebo (Fig. 2).

The mortality rate (%) recorded after different antiviral drug treatments was represented in Fig. 3. Administration of Remd reduced the mortality rate significantly ($p<0.05$) compared to placebo. However, other treatments did not alter the mortality rate significantly compared to placebo.

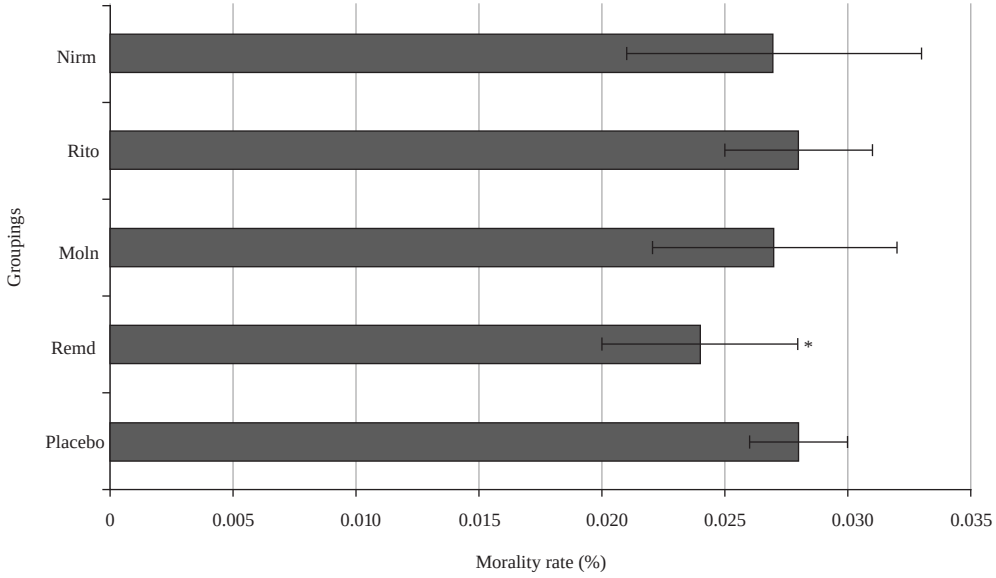

Fig. 3: Mortality rate recorded after administration of different antiviral drugs

Remd: Remdesivir, Moln: Molnupiravir, Rito: Ritonavir, Nirm: Nirmatrelvir, values are represented as mean±SD, Statistics: One-way ANOVA followed by Mann-Whitney U Test and *p<0.05 compared with placebo

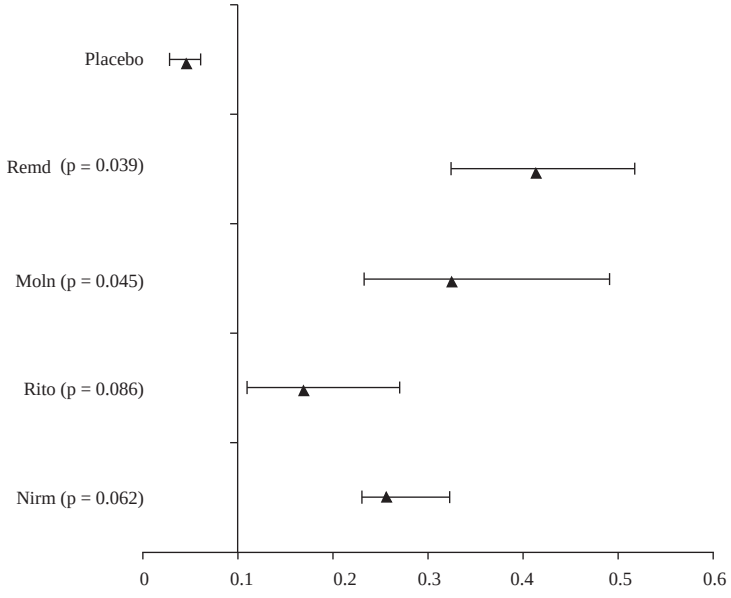

Fig. 4: Forest plot of logistic regression analysis for incidences of side effects after antiviral drug treatment

Remd: Remdesivir, Moln: Molnupiravir, Rito: Ritonavir, Nirm: Nirmatrelvir, Statistics: One-way ANOVA and Chi-square Test and p-value indicates a comparison with placebo

Logistic regression analysis of the data recorded for incidences of side effects after administration of different antiviral treatments was indicated in Fig. 4. Analysis of the results suggests that the odd ratios for Remd (OR = 0.41, p = 0.039, 95% CI = 0.106/0.086) and Moln (OR = 0.31, p = 0.045, 96% CI = 0.18/0.077) were significantly varied compared to placebo. The odd ratio for Rito and Nirm was 0.18 and 0.26, respectively. The p-values for Rito (p = 0.086, 95% CI = 0.089/0.069) and Nirm (p = 0.062, 95% CI = 0.063/0.029) were not found to vary significantly upon comparison with placebo.

Table 4: Common gastrointestinal, metabolic and immunological side effects observed after antiviral drug treatment

	Gastrointestinal				Metabolic		Immunology	
Treatment	Diarrhea	#Change (%)	Constipation	#Change (%)	Hyperglycemia	#Change (%)	Hypersensitivity	#Change (%)
Placebo	1.18±0.45		2.88±0.63		0.36±0.04		1.31±0.21	
Remd	1.45±0.56*	22.88	2.23±0.56	-22.57	0.31±0.09	-13.89	1.70±0.36**	29.77
Moln	1.29±0.71	9.32	3.29±0.72*	14.23	0.38±0.10	5.55	1.65±0.25**	25.95
Rito	1.31±0.39	11.10	3.11±0.52	7.8	0.39±0.07	8.33	1.28±0.44	-2.33
Nirm	1.69±0.68**	43.22	2.92±0.61	1.38	0.32±0.08	-11.12	1.58±0.59*	20.61

Remd: Remdesivir, Moln: Molnupiravir, Rito: Ritonavir and Nirm: Nirmatrelvir, values are represented as Mean±SD, Statistics: One-way ANOVA followed by Mann-Whitney U Test,*p<0.05, **p<0.01 compared with placebo and #Percentage change when compared to placebo

DISCUSSION

The present study examined the safety of four antiviral drugs such as Remd, Moln, Rito and Nirm, using the most commonly observed side effects according to important systems of the body. These drugs were approved for the first time in Saudi Arabia to treat the complicated cases of patients diagnosed with COVID-19. In the event of several complicated adverse events reported from different classes of antiviral drugs, the study assumes the importance of summarizing the safety profile of the antivirals recommended for COVID-19.

The drugs were tested in different groups of the population aged above 18 years (since some drugs, such as Moln are not yet approved for less than 18 years population)[24] and included both male and female gender participants (Fig. 1). Analysis of table data suggested that none of the tested antiviral drugs altered the rhythmicity of the heart when compared with a placebo. Further, administration of Nirm was found to increase significantly ($p<0.05$) the blood pressure compared with placebo. Earlier studies have suggested that elevation in blood pressure is mediated through several mechanisms, such as adrenergic activation, retention of fluids and salts, neurogenic stimulation and vascular muscle defects[25]. Studies conducted in the past have reported that administering medications such as antivirals can increase blood pressure. The reason was identified to be either increased retention of fluids and salts and/or due to stimulation of cardiac muscle activity[26].

In addition, Rito was found to increase significantly ($p<0.05$) the anemic condition in patients (Table 1). Similar observations were recorded in the literature, where administering antivirals such as Rito has produced conditions like anemia[27]. The results indicated that this action might be related to the mechanism of action of the drug. Rito being an inhibitor of nucleic acid synthesis, might have exerted this action on the proliferation of blood cells and might have interfered with the erythropoiesis[28]. Besides, studies have suggested that antivirals tend to cause hemolysis as a side effect in patients. This action is also suggested to be due to the interference of antivirals in nucleic acid synthesis[29].

In the nervous system, the data from the present study suggested that Remd significantly ($p<0.05$) increased the frequency of anxiety in the patients (Table 2). As reported in the literature, the pathogenicity of anxiety is related to disturbances in the level of biogenic amines in the central nervous system[30]. Drugs used in infectious diseases have been reported to alter psychological activity by changing the levels of monoamines in the brain[31]. However, the findings might contradict the earlier results where Remd was found to induce non-significant variation in the behavior of the patients[32]. This evidence suggested that antimicrobials might produce symptoms characteristics of anxiety[33]. Further, Remd and Moln were found to produce significant ($p<0.05$) apnea compared with placebo (Table 2). Apnea is reported to occur due to several causes, such as being overweight, obesity, inherited narrow throat, aged people, hypersensitivity and under sedatives[34,35]. Since Remd and Moln, in earlier studies, are reported to cause hypersensitivity in patients, the increased frequency of apnea observed in this study could be related to the immunological reactions[36,37].

Among different antiviral drugs tested, Remd was found to increase significantly ($p<0.05$) the ALT levels and induced hepatitis when compared with placebo (Table 3). These changes are in accordance with the previous studies that Remd treatment is associated with increased ALT levels[38]. Additionally, these hepatic alterations are reported to depend on several factors, such as dose, duration of therapy, age of patients and comorbidities[39]. As recommended, Remd is not prescribed to all patients diagnosed with COVID-19. Careful monitoring of ALT levels is required in COVID-19 patients since the infection itself is reported to elevate the transaminase levels[40]. The dosage and selection of patients for Remd must strictly be monitored. Aged and patients with elevated ALT levels are either contraindicated or closely observed for symptoms of liver damage[41]. Further, administration of Moln was observed to cause oliguria significantly ($p<0.05$) in

patients compared with placebo (Table 3). Oliguria, as reported in previous studies, occurs due to low blood volume, heart/lung condition and vascular diseases of the kidney[42]. Antiviral therapy in earlier studies has been reported to cause a lowering of blood volume and alteration of kidney vasculature[43]. These changes might have also occurred when Moln was tested, resulting in oliguria in patients.

The two common gastrointestinal side effects observed in the study are diarrhea and constipation. The Remd and Nirm have enhanced the incidences of diarrhea, while Moln produced constipation in patients (Table 4). Normally, these side effects are related to gastrointestinal smooth muscle physiology. Any alteration in the peristaltic activity is reported to either increase motility (diarrhea) or decrease it (constipation)[44]. Antiviral drugs in earlier studies are reported to modify the functioning of gastrointestinal smooth muscles. These side effects are routinely observed with therapeutic interventions[45]. Remd, Nirm and Moln might have induced changes in the peristaltic movements of gastrointestinal muscles to induce either hypermotility or hypomotility. Further, the tested antivirals did not induce significant alteration in the blood glucose level. However, in the immunological system, Remd, Moln and Nirm were found to produce significant ($p<0.05$) allergic reactions when compared with placebo (Table 4). As reported in the literature, hypersensitivity reaction is mediated by the immunological cells. The reaction between the antigen and antibody gets exaggerated, leading to allergies[36]. The observation from the present study is in accordance with the earlier findings. Antivirals in other studies too, have been reported to cause hyperactivation of immune cells and produce hypersensitivities[46].

Figure 2 and 3 indicated that although Remd had higher incidences of serious adverse events but also reduced the mortality rate significantly ($p<0.05$) compared to placebo. The higher incidences of serious adverse events are likely related to hypersensitivities and hepatic dysfunction by Remd. The studies conducted in the past support that compounds having such characteristics could induce serious adverse events in patients[47]. On the other hand, the reduction in mortality rate could be linked to the antiviral property of Remd wherein the administration reduced the viral load in COVID-19 patients and enhanced their survival rate by managing the complications of the disease[48].

The logistic regression analysis forest plot indicated that the odd ratios for Remd, Moln, Rito and Nirm were 0.41, 0.31, 0.18 and 0.26, respectively. The observations suggest that the administration of Rito and Nirm have a weak association with the incidences of observed side effects. In contrast, Moln had a mild correlation and Remd had a mild-moderate association (Fig. 4). The data analysis with previous studies suggests that most of these side effects are routinely observed with medical interventions[49]. Drugs being chemicals, were found to beneficial therapeutic action[50]. The data from the study might assist healthcare providers in weighing the benefits of antivirals according to side effects observed in different systems and selecting the specific agent based on the patient's need and past medical history.

Although the infection rate of COVID-19 has significantly receded, the pandemic is not yet over, as incidences of the spread of several variants of COVID-19 are still being reported from different regions of the world. Without a specific, safe and efficacious therapeutic intervention, research is conducted at a war-footing pace to defeat COVID-19. Antiviral medications have the advantage of targeting the specific site of viral replication and, in earlier incidences of viral spread, too, were found to be efficacious in treating the infection. However, these medications are associated with several unexpected side effects, creating apprehensions about the impact of therapy on the public.

The present study analyzed the most common side effects of antiviral drugs. The data represented in the study is the mean of incidences of the selected side effects retrieved from the published journals. Other serious side effects might be specific for different antiviral agents, such as teratogenicity, mutagenicity, carcinogenicity and impairment of fertility. These potential adverse effects are under study at various stages of testing. Hence, there is a need to update the information on the side effects of antiviral drugs recommended for COVID-19.

CONCLUSION

The present study evaluated the common side effects of antiviral drugs such as Remd, Mol, Rito and Nirm approved in Saudi Arabia. Although most of the side effects observed are routinely recorded with any therapeutic agents, hypertension with Nirm, anemia with Rito, oliguria with Moln and hepatitis and anxiety with Remd need to be carefully monitored since these effects might interfere with the prognosis of the therapy. The most appropriate option is to avoid the medications in patients who have a previous history of these or related diseases. More research and regular safety updates are essential to evaluate the long-term effect of antiviral drugs.

SIGNIFICANCE STATEMENT

The present study analyzed the safety profile of four antiviral agents approved in Saudi Arabia for treating complicated cases of Coronavirus Disease 2019 (COVID-19). Comprehensive data from the literature was statistically (Moln), ritonavir (Rito) and nirmatrelvir (Nirm). Results indicated a significant ($p<0.05$) increase in adverse effects with Remd (mild to moderate correlation with anxiety, apnea, hepatitis and hypersensitivity), Moln (mild correlation with apnea and hypersensitivity), Rito (weak correlation with anemia) and Nirm (weak correlation with hypertension and hypersensitivity) compared to placebo. In the event of incidences of adverse effects, caution needs to be followed while treating COVID-19 with these antiviral agents, especially in patients having a past medical history of hypersensitivity, hypertension, hepatitis, anxiety and apnea.

ACKNOWLEDGMENT

The authors thank AlMaarefa University, Riyadh, Saudi Arabia, for extending financial support for this research.

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