wjpmr, 2025, 11(10), 176-182

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH
www.wjpmr.com

SJIF Impact Factor: 6.842

Review Article

ISSN (O): 2455-3301

ISSN (P): 3051-2557

ANALYSIS OF SUSPECTED ADVERSE DRUG EVENTS OF ANTIVIRAL DRUGS USED IN COVID-19: A REVIEW

Dr. T. Peter*

Assistant Professor in Pharmacology, College of Pharmacy, Madurai Medical College, Madurai. The Tamil Nadu Dr.MGR. Medical University, Chennai, Tamil Nadu, India.

***Corresponding Author: Dr. T. Peter**

Assistant Professor in Pharmacology, College of Pharmacy, Madurai Medical College, Madurai. The Tamil Nadu Dr. MGR. Medical University, Chennai, Tamil Nadu, India. **DOI:** https://doi.org/10.5281/zenodo.17224623

Article Received on 12/08/2025 **Article Revised on 01/09/2025** **Article Accepted on 22/09/2025**

ABSTRACT

COVID-19 is an infectious disease caused by a novel coronavirus [SARS-CoV-2]. The COVID19 pandemic was declared by the World Health Organization (WHO) on 11 March 2020. So many drugs have been used to treat COVID-19 patients. During the course of treatment, patients are experienced adverse drug reaction despite of beneficial effect of drug. But there is not even one drug have shown 100% therapeutic benefit in COVID-19 patients. Adverse drug reactions are major global public health problem and an important cause of mortality. In this review study, I know impact of adverse drug reaction in COVID - 19 patients. Especially focused on Antiviral drugs such as Lopinavir/Ritonavir, Ribavirin, Remdesivir and Favipiravir used to treat COVID19.

KEYWORDS: COVID-19, Antiviral drugs, adverse drug events.

INTRODUCTION

COVID-19 originated in Wuhan, China, in late 2019 and In India, Covid-19 was discovered in Kerala (27-1-2020) and declared a global pandemic by WHO on March 12, 2020.[1,2] It is caused by SARS-CoV-2.[3] Over nine months, COVID-19 significantly increased global morbidity and mortality.[4] Preventive measures include hygiene, social distancing, quarantine, and containment.[5] Researchers are repurposing antiviral therapies, though no clinically effective drug currently exists.[6] Various categories of drugs used for the treatment of Covid-19 are Hydroxychloroquine, Ivermectin, Azithromycin, Dexamethasone, Paracetamol, Doxycycline, Amphotericin, etc. Each drug has several adverse drug reactions and then later introduced antiviral drugs such as Lopinavir /ritonavir Ribavirin, Remdesivir & Favipiravir and 3 adjunctive therapies that warrant special mention are corticosteroids, anti-cytokine or immunomodulatory agents, and immune globulin therapy. 58 drugs are used in Covid-19 treatment; these drugs also produce so many adverse drug reactions. So we planned to study was undertaken to analysis the suspected adverse reactions of antiviral drugs used in Covid-19 treatment. Lopinavir-ritonavir, used for HIV, is suggested as a treatment.[7] Lopinavir inhibits SARS-CoV, SARS-CoV-2, and MERS-CoV in vitro.[8] Ribavirin, used for hepatitis C and MERS, is suggested with interferon or lopinavir/ritonavir[9], remdesivir reduces recovery time in severe cases but showed no significant mortality benefit.[10] Favipiravir, effective against Ebola and influenza, shows promise against SARS-CoV-2 with minimal adverse effects but is advised for limited use.[11]

METHODS

The data were collected from WHO database, google, research gate, Elsevier, springer, etc. A literature review was performed using PubMed to identify relevant English-language articles and retrieved all the articles published in English language that reported pharmacology, clinical outcome and adverse drug reactions in patients with COVID-19.

ANTIVIRAL DRUGS

Anti-viral drugs are agents used to treat against virus. Some of the Anti-retroviral drugs are being used in treatment of covid-19. For ex: Lopinavir /ritonavir come under the class that inhibits 3-chymotyrpsin like protease inhibitor; Ribavirin, Remdesivir & Favipiravir inhibits viral RNA dependent RNA polymerase; Arbidol targets S protein /ACE2 interaction leads to inhibit membrane fusion of the viral envelope; Camostat mesylate inhibits TMPRSS2 leads to prevent viral cell entry.

Lopinavir/Ritonavir

Lopinavir/ritonavir, a US Food and Drug Administration (FDA) - approved oral combination agent for treating HIV, demonstrated in- vitro activity against other novel corona viruses via inhibition of 3-chymotrypsin-like protease.[12,13] The most commonly used and studied lopinavir/ritonavir dosing regimen for COVID-19 treatment is 400mg/100mg twice daily for up to 14

days.[14,15] It is administered by oral route. It is metabolised in liver.[13] Drug-Drug Interaction: CYP3A4 inhibitor and substrate; CYP2D6 substrate; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 Inducer, P-gp substrate; UGT1A1 inducer.

Ribavirin

Ribavirin is a guanine analogue. It inhibits viral RNA-dependent RNA polymerase. Most common therapeutic use of oral ribavirin is in chronic hepatitis C. Nebulized ribavirin is used for respiratory syncytial virus bronchiolitis in infants and children. Ribavirin has shown efficacy in some rare viral infections as well. Its activity against other nCoVs makes it a candidate for COVID-19 treatment. However, its in-vitro activity against SARS-CoV was limited and required high concentrations to inhibit viral replication, necessitating high-dose and combination therapy. 1.2 g to 2.4 g orally every 8 hours. Patients received either intravenous or enteral administration in previous studies.[16] Oral bioavailability of ribavirin is - 50%. 1t is partly metabolized and eliminated mainly by the kidney.

Remdesivir

Remdesivir, formally known as GS-5734, is a monophosphate prodrug that undergoes metabolism to an active C-adenosine nucleoside triphosphate analogue. It produces the activity against RNA viruses, such as Corona viridae and Flaviviridae.[17] Remdesivir is a promising potential therapy for COVID-19 due to its broad-spectrum, potent in vitro activity against several nCoVs[18,19] Intravenous infusions between 3 mg and 225 mg were well-tolerated. The current dose under investigation is a single 200 mg loading dose, followed by 100 mg daily infusion.[20]

Favipiravir

Favipiravir, previously known as T-705, is a prodrug of a purine nucleotide, with active metabolite favipiravir ribofuranosyl-5′-triphosphate. The active metabolite (T-705-RTP) blocks the RNA-dependent RNA polymerase action, then halting the viral replication.[21] It is administered by oral and intravenous route. A loading dose is recommended (2400 mg to 3000 mg every 12 hours × 2 doses) followed by a maintenance dose (1200 mg to 1800 mg every 12 hours). It is excreted through liver, kidney and intestine. The half-life is approximately 5 hours.[22]

RESULTS

Lopinavir/Ritonavir

Outcomes were assessed at 28 days after randomisation, with further analyses specified at 6 months. The primary outcome was 28-day mortality. Secondary outcomes were time to discharge from hospital within 28 days and among patients not on invasive mechanical ventilation at randomisation, receipt of invasive mechanical ventilation or death.[23]

The following adverse drug events of Lopinavir and Ritonavir given in Table No.1.

Table 1: ADEs of Lopinavir and Ritonavir.

S. NO.	ADEs	Reports
1	Diarrhea	49
2	Hypertriglyceridemia	28
3	Hepaticenzymeincreased	21
4	ElectrocardiogramQTprolonged	20
5	Transaminase increased	10
6	Hypercholesterolemia	4

Ribavirin and Interferon (Adverse Events)

Ribavirin and Interferon-Associated Adverse Events: During the study period, a total of 2200 adverse event reports were reported with ribavirin and interferon as the first suspected drugs. All the detected adverse event reactions were associated with 13 SOC (system organ classes), such as gastrointestinal, blood and lymph, hepatobiliary, endocrine, and various nervous systems. The results showed that females were more likely to suffer from anaemia, vomiting, neutropenia, diarrhoea, and insomnia than males.[24]

Table No. 2 All detected adverse drug events for Ribavirin according to SOC and PT.

Adverse Drug Events (PT)	Reports
Blood and lymphatic system disorders	
Anaemia	256
Neutropenia	87
Endocrine disorders	
Hypothyroidism	31
Thyroid disorder	22
Hyperthyroidism	18
Eye disorders	
Visual acuity reduced Retinal	23
exudates	13

Gastrointestinal disorders	
Vomiting	107
Diarrhoea	85
Abdominal pain	39
Ascites	31
Abdominal distension	26
Haemorrhoids	22
Mouth ulceration	14
Tooth loss	9
Irritable bowel syndrome	8
Psychiatric disorder	
Depression	149
Insomnia	81
Anorexia	35
Suicidal ideation	30
Psychotic disorder	16
Renal and urinary disorder	
Renal impairment	18
Respiratory and thoracic disorders	
Intestinal lung disease	13
Haemoptysis	9
Skin and subcutaneous tissue disorders	
Rash	173
Pruritus	113
General disorders	
Oedema peripheral	29
Hepatobiliary disorders	
Hepatic cirrhosis	56
Hepatic failure	34
Hepatic fibrosis	23
Hepatotoxicity	9
Investigations	
Platelet count decreased	80
WBC count decreased	79
Haemoglobin decreased	72
RBCcount decreased	25
Metabolism and nutrition disorders	
Dehydration	42
Diabetes mellitus	30
Lacticacidosis	10
Nervous system disorders	
Loss of consciousness	28
Dysgeusia	21
Cerebral infarction	18

Remdesivir

They conducted a chart review of the entire sample of 149 participants. Of these, 101 were on an HCQ regimen (400 mg on day 1, followed by 200 mg twice daily for 5–10 days) while the remaining 48 took REM (200 mg on day 1 followed by 100 mg once daily for 5 or 10 days). ADR incidence was significantly higher in the HCQ cohort than in the REM cohort. Of the 149 patients, 54 had one or more suspected ADRs. Hepatobiliary disorders were identified in 43 patients corresponding to the most common ADR, followed by gastrointestinal, renal and cardiac disorders. Within hepatobiliary disorders, transaminase increase was present in 51.2% of patients. Except for ADRs relating to nervous system disorders, which were reported only once in the REM cohort, the ADR incidence was greater in the HCQ group, which included QT interval prolongation in six patients and atrial fibrillation in two patients.[25] They will first summarize reported ADE in the published studies as well as summaries provided by Gilead to the regulatory authorities before documenting the ADEs reported to VigiBase. There was a total 1087 ADEs reported from the 439 case information reports. 35 Each case information report represents one person was given remdesivir. After removal of duplicate ADEs, 1004 unique ADEs were available for the analysis.[26] ADEs suspected to be caused by remdesivir reported in 439 individuals in WHO database in the following table No.3.

Table No. 3: ADEs suspected to be caused by remdesivir reported in 439 individuals in WHO database.

S. NO.	ADEs	Frequency (%)
1	Hepaticenzymeincreased	141
2	Renal injury	63
3	Blood creatinine increased	49
4	Medication Error	34
5	Product use in Unapproved Condition	29
6	Respiratory failure	28
7	Tachy or Bradyarrhythmia	26
8	Hypotension	24
9	Rash	22
10	Therapy cessation	19
12	Condition Aggravated/Disease Progression	18
13	Sepsis and Septic Shock	17
14	Cardiac and Cardiorespiratory Arrest	15
15	Nausea and Vomiting	14
16	Glomerular filtration rate decreased	14
17	Renal impairment	13
18	Abnormal Hemogram	13
19	Renal failure	12
20	Death	11
21	Multiorgan Disorder/Organ Failure	11
22	Pyrexia	11
23	Hypoxia	11
24	Dialysis	10
25	Diarrhoea	10
	Acidosis	

Favipiravir

Most frequent adverse events suspected to be caused by the favipiravir were increased in the hepatic enzymes, nausea and vomiting, tachycardia, and diarrhoea. Skin and subcutaneous tissue disorders and gastrointestinal disorders were more prevalent, while blood and lymphatic disorders and nervous system disorders were less prevalent among those aged below 64 than among those aged 64 and above. Severe ADEs were more prevalent in males than females. Blood and lymphatic disorders, cardiac disorders, hepatobiliary disorders, injury poisoning, and procedural complications were more common in those with severe ADEs than those with non-serious ADEs. All fatal ADEs were severe, and most non- serious ADEs were not mentioned.[27] Adverse drug events caused by Favipiravir, as reported in the WHO Data base in the following table. No.4.

Table No. 4: Adverse drug events caused by Favipiravir, as reported in the WHO database.

AdverseDrug Events	Frequency
Intestinal product use issue	65
Hepatic enzyme increased	22
Nausea and vomiting	13
Tachycardia	9
Diarrhoea	7
ECG-QT prolonged	5
Headache	5
Pruritus	5
Rash	5
Erythema	5
Hepatotoxicity	4
Thrombocytopenia	4
Bradycardia	4
Abdominal pain	3
Constipation	2
Hypotension	2
Anaemia	2
Acute kidney injury	2
Arthritis	1
Atrial fibrillation	1

Bronchospasm	1 1
Colitis	1
Cough	1
Cystic fibrosis	1
Death	1
Dizziness	1
Dyspnoea	1
Haemorrhage	1
Hair colour changes	1
Hyperglycaemia	1
Hypertension	1
Leukopenia	1
Muscle contraction involuntary	1
Musculoskeletal pain	1
Nail discolouration	1
Palpitations	1
Pyrexia	1
Respiratory distress	1
Rhabdomyolysis	1
Seizure	
Syncope	
Urticaria	
Vasculitis	
Visual impairment	

DISCUSSION

Antiviral and antiretroviral medications also took their turn as experimental treatments. Lopinavir/Ritonavir was one of these tried and the common side effects include GI symptoms as well as headache, drowsiness or dizziness.[28] The monotherapy of Lopinavir/Ritonavir is not an effective with COVID-19 patients, but combination of Lopinavir – Ritonavir has been recommended as a first – line or second – line used in many countries.[29]

Ribavirin early bench work had shown promising lack of effective in-vitro activity against SARS-COV2 unless when give high doses were employed significant hematologic side effects were seen in SARS and MERS trials. When Ribavirin and Interferon are co-administered in patients with COVID-19, close monitoring of the haemoglobin level is recommended. In another study, a case of death due to combined treatment was reported.[30] At the start of treatment, the patients already had a rather low platelet count; the platelet further drops after the combined treatment and finally leads to death. At present studies the combination treatment of drugs confirmed increase the risk of diseases such as depression and anxiety.[31]

Remdesivir showed in vitro testing on SARSCoV-2 common reactions include GI symptoms and hyperglycaemia while some of the more serious effects are acute kidney injury, AST/ALT elevation and seizures.[32]

Favipiravir is not recommended in pregnancy due to teratogenic risks in the preclinical studies.[33] Studies conducted on favipiravir for COVID-19 treatment appears to be a relatively safe drug.[28] Recommendations needed clinicians using favipiravir should monitoring for the hepatic enzyme rise, ECG changes, and drug interactions during treatment to avoid ADE and attain preferable clinical outcomes.[34]

Table 5: Discussion of Toxicities of Antiviral drugs used in treatment of COVID-19.

S.No.	Drug	Dose/Administration/ Drugformulation	AdverseDrug Reactions
1.	Lopinavir/ Ritonavir	400 mg/100 mg (Tablet) by mouth every12hours for upto 14 days.	Common: Gastrointestinal intolerance, nausea, vomiting, diarrhoea. Major: Pancreatitis, Hepatotoxicity, Cardiac conduction abnormalities.
2.	Ribavirin	Highdose, 1.2g to 2.4g (Capsule) orally for every 8hours.	Hematologic and Liver toxicity.
3.	Remdesivir	200mg for 1 day, 100mg every 24hours IVinfusion. (injection)	Elevated transaminases (reversible), Kidney injury.
4.	Favipiravir	Dose varies based on indication. Available as 200 mg tablet.	Hyperuricemia, Diarrhoea, elevated transaminases, reduction in neutrophil count

CONCLUSION

The COVID-19 pandemic represents the greatest global public health crisis of this generation and potentially since the pandemic influenza outbreak of 1918. SARS-CoV-2 is a novice virus, researchers worldwide are still decoding the virus and the pattern of the human body's biochemical and pathological changes brought about by SARS-CoV-2. ADRs have a perspective to provoke harmful effects in patients. Healthcare workers and pharmacovigilance constrain being conscious of perceive the ADRs in the patient. Many new drugs and already available drugs are repurposed to treat COVID-19. Every healthcare professional should see it as parts of his/her professional duty keeping in mind about "Hippocrates admonition" at least do no harm. Past few years many variants are developed. So, no therapies have been shown 100% effective. These drugs are used for symptomatic treatment.

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