The Intercontinental Journal of
Internal Medicine

DOI: 10.51271/ICJIM-0026

Review

COVID-19 infection: antiviral therapy

Hakkı Öztürk[1], Metin Özsoy[2]

[1]Infectious Diseases Epidemiologist, Private Ankara Dialysis Center, Ankara, Turkiye
[2]Department of Infectious Diseases and Clinical Microbiology, Ankara Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

Cite this article: Öztürk H, Özsoy M. COVID-19 infection: antiviral therapy. *Intercont J Int Med.* 2024;2(1):12-16.

Corresponding Author: Hakkı Öztürk, ozturk_h@msn.com

Received: 03/02/2024 ◆ **Accepted**: 24/02/2024 ◆ **Published**: 29/02/2024

ABSTRACT

This review summarizes the current literature on antiviral drugs used in the treatment of coronavirus disease 2019 (COVID-19). The pandemic caused by COVID-19 is an important cause of mortality and morbidity all over the world and in Turkey. COVID-19 infection is a viral infection caused by the SARS-CoV-2 virus that can affect many organs, such as the heart, gastrointestinal system, and central nervous system, especially the lungs. Many anti-microbials have been tried in the treatment of COVID-19 in the past few years. Today, there are some antiviral drugs that have clinically proven efficacy in the treatment of COVID-19 and are still in use.

Keywords: COVID-19, SARS-CoV-2, clinical trials, current treatment, antiviral drugs

INTRODUCTION

The disease caused by SARS-CoV-2 has been named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). It can cause respiratory illnesses ranging from mild symptoms to serious ones. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is in the genus Betacoronavirus, family *Coronaviridae*.[1] It was declared a "pandemic" by the World Health Organization (WHO) in March 2020. Since then, numerous clinical and experimental studies have been conducted to determine effective approaches for prevention and treatment.[2,3]

According to the data from the Ministry of Health, 17,232,066 confirmed COVID-19 cases and a total of 102,174 deaths due to COVID-19 were reported in Turkey until March 2023.[3] According to the data of the Ministry of Health, a total of 152,725,380 doses of the COVID-19 vaccine were administered until September 24, 2023, and the number of people who received a single-dose vaccine was 57,959,115, while the number of people who received a double-dose vaccine was 53,194,534.[4,5] According to the World Health Organization's report dated January 15, 2024, 701,742,393 confirmed cases, 6,968,842 deaths due to COVID-19, and 672,730,354 cases recovered from COVID-19 were reported worldwide.[4]

COVID can present with many different clinical presentations. Main clinical symptoms of the COVID-19 infection include fever, cough, shortness of breath, and chest pain. These symptoms may be accompanied by headaches, sore throats, and taste and smell disturbances. The most common imaging finding in viral pneumonia caused by COVID-19 is the detection of bilateral peripherally located ground-glass opacities on computed tomography (CT) imaging. Although COVID-19 mostly involves the lungs, involvement of the cardiovascular system, gastrointestinal system, and central nervous system can also be observed. WHO estimates that about 80% of COVID-19 cases recover without the need for hospital treatment, 15% become seriously ill and require oxygen (O2), and about 5% of cases require intensive care. The main cause of death in COVID-19 patients leads to a "cytokine storm syndrome" responsible for organ damage, acute respiratory distress syndrome (ARDS), and respiratory failure. The primary site of SARS-CoV-2 morbidity is the respiratory tract. However, extrapulmonary manifestations affecting the heart, liver, kidneys, brain, intestine, pancreas, testes, ovaries, breast, uterus, and placenta are also common. This can be attributed to the high expression of angiotensin-converting enzyme-2 (ACE-2) in these tissues. Another important mechanism underlying the pathophysiology of multi-organ damage secondary to SARSCoV-2 infection involves direct viral endothelial damage, which can induce inappropriate thrombin generation by inhibition of fibrinolysis and activation of complement pathways, triggering microthrombi accumulation and microvascular dysfunction.[2]

Many anti-bacterial, anti-parasitic, and anti-viral drugs have been tried in the treatment of COVID-19 in the past few years. Some antiviral drugs with proven efficacy are currently used in the treatment of COVID-19. In the past years, chloroquine, hydroxychloroquine, ivermectin, and nitazoxanide were among the parasitic drugs; azithromycin was among the antibacterial drugs; and lopinavir/ritonavir, ribavirin, darunavir-cobicistat, umifenovir, favipiravir, and remdesivir were among the antiviral drugs used in the treatment of COVID-19.[3,6,7] In the COVID-19 pandemic, the development and widespread use of inactivated vaccines and mRNA vaccines, as well as the use of antiviral drugs effective against SARS-CoV-2, contributed to the decrease in SARS-CoV-2-related mortality and morbidity rates.

This work is licensed under a Creative Commons Attribution 4.0 International License.

In this article, antiviral drugs currently used in the treatment of COVID-19 disease and clinical and in vitro studies with these drugs are summarized.

ANTIVIRAL DRUGS IN COVID-19

Antiviral agents reported against COVID-19 mainly include polymerase inhibitors, protease inhibitors, nucleoside and nucleotide reverse transcriptase inhibitors, entry and uncoating inhibitors, and other antivirals (Table 1).[8]

Table 1. Antiviral drugs used to treat COVID-19

Polymerase inhibitors
..... Remdesivir
Molnupiravir
Paxlovid (nirmatrelvir/ritonavir)
Old antiviral drugs
.....Favipiravir
Lopinavir/ritonavir
Pegylated interferon Lambda

Antiviral drugs act by interfering with the SARSCoV-2 replication cycle to reduce viral load and its subsequent pathological effects. Mechanisms of action include inhibition of virus entry via the ACE2 receptor and/or TMPRSS2, viral membrane fusion and endocytosis, or viral proteases and RdRp. This class of drugs has a vital role in preventing the progression of COVID-19 disease because viral replication is more active during early infection.[2]

Polymerase Inhibitors

Remdesivir: Remdesivir is the first antiviral drug approved by the FDA for COVID-19. It is a nucleotide analog prodrug. Its active metabolite, an adenosine analog, can bind to viral RNA-dependent RNA polymerase (RdRp) and inhibit viral replication by causing premature termination of RNA transcription.[2]

It has a broad spectrum of antiviral in vitro activity against other pathogenic RNA viruses, including Middle East respiratory syndrome (MERS), SARS-CoV-1, and bat CoV viruses. The World Health Organization (WHO) issued a conditional recommendation in 2020 against the use of remdesivir in hospitalized patients regardless of severity of illness, despite the lack of sufficient evidence at the time that remdesivir could improve survival or other clinical outcomes. The WHO recommendation reported that there was insufficient evidence to support the use of remdesivir.[3]

Later, in April 2022, following the emergence of new data from clinical trials, WHO updated its recommendations and recommended the use of remdesivir in mild or moderate COVID-19 patients at high risk of hospitalization.[2]

In a clinical trial of non-hospitalized COVID-19 patients, safety was found to be acceptable after 3 days of remdesivir treatment, while the risk of hospitalization or death was reported to be reduced by 87% compared to placebo. Another clinical trial reported that remdesivir outperformed placebo.

It was also reported that adults hospitalized for COVID-19 and lower respiratory tract infections had a shorter recovery time after receiving remdesivir treatment. In contrast to these studies, multicenter studies in China reported no statistically significant difference in the clinical condition of COVID-19 patients receiving remdesivir compared to standard care. In addition, it was reported that remdesivir combined with baricytinib, a Janus kinase inhibitor, was more effective than remdesivir alone in terms of shortening the recovery time of COVID-19 patients and accelerating the improvement of their clinical symptoms.[8]

The US Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Infectious Diseases Society of America (IDSA), and the National Institute for Health and Clinical Excellence (NICE) in their latest guidelines recommend the use of remdesivir in hospitalized and non-hospitalized adult and pediatric patients (age ≥28 days and body weight ≥3 kg) with "mild to moderate COVID-19." In addition, to reduce the risk of disease progression, the NIH recommends co-administration of remdesivir with dexamethasone for hospitalized COVID-19 patients requiring O2 supplementation. Remdesivir is administered intravenously (IV) over 30-120 minutes at a dose of 200 mg (loading dose) on day 1, followed by a maintenance dose of 100 mg/day. For pediatric patients (less than 40 kg), the loading dose on day 1 is 5 mg/kg, followed by a maintenance dose of 2.5 mg/kg/day.[2] The recommended total duration of treatment for non-hospitalized patients is 3 days. In hospitalized patients, it is 5 days or until the patient is discharged. However, if the patient does not improve clinically, the clinician may extend the treatment period up to 5 days, and the total treatment period should not exceed 10 days.[9]

The most common side effect of remdesivir is nausea. It may also increase liver transaminases and prothrombin time and cause hypersensitivity reactions. Chloroquine and hydroxychloroquine reduce the antiviral activity of remdesivir; therefore, they are not recommended to be administered together. The dose of Remdesivir should be adjusted for patients with renal impairment. It is not recommended for use in patients with a glomerular filtration rate (eGFR)<30 ml/min. Remdesivir is well tolerated during pregnancy, and the rate of serious side effects is low.[2]

Molnupiravir: Molnupiravir is another oral antiviral drug that targets viral replication. It is a prodrug that joins viral RNA strands mimicking the nucleoside cytidine or uridine and is converted to β-D-N4-hydroxycytidine (NHC), leading to 'error catastrophe' during viral replication.[2]

Molnupiravir, an oral prodrug of N-hydroxycytidine, has previously demonstrated a high barrier to resistance development with broad in vitro antiviral activity against multiple RNA viruses.[10]

It has activity against coronaviruses, including SARS-CoV-2. It has been reported to reduce the risk of hospital admission or death by approximately 50% in non-hospitalized COVID-19 patients. A study to evaluate the efficacy and safety of molnupiravir treatment in non-hospitalized, unvaccinated adults with mild-to-moderate COVID-19 suggested that the risk of hospitalization or death due to COVID-19 in unvaccinated adults may be reduced by early treatment with molnupiravir. Another study reported that molnupiravir was active against the three dominant circulating variants of SARS-CoV-2 (delta, gamma, and mu) and showed a moderate antiviral effect.[8]

Molnupiravir was also tested in prophylaxis after domestic contact with patients with COVID-19. In the study, COVID-19 infection rates up to day 14 were 6.5% in those receiving molnupiravir prophylaxis and 8.5% in those receiving placebo, with no statistically significant differences

reported. Although molnupiravir was well tolerated in prophylaxis, it was reported that its failure to meet the predetermined superiority criterion may be partially affected by the pre-existing high immunity in the study population.[11]

The FDA, NIH, IDSA, and NICE guidelines recommend the use of molnupiravir in non-hospitalized adult patients with "mild to moderate COVID-19" to reduce the risk of disease progression "only when Paxlovid or remdesivir cannot be used." The dose of molnupiravir is 800 mg orally every 12 hours for 5 days, starting within 5 days of symptom onset.[2,11]

Strizki et al.[10] evaluated the antiviral activity and potential for resistance development of molnupiravir against SARS-CoV-2 omicron variants (BA.1, BA.1.1, BA.2, BA.4, BA.4.4.6, BA.5, BQ.1.1, XBB.1 and XBB.1.1.5), alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), lambda (C.37), and mu (B.1.621) variants in Vero E6 cells using cytopathic effect assays. In the study, it was reported that molnupiravir maintained antiviral activity in all major SARS-CoV-2 variants and no viral resistance to this drug was detected; therefore, molnupiravir has a high barrier to resistance development.

The most common side effects of molnupiravir are nausea, diarrhea, and dizziness. Neither drug interactions nor contraindications have been reported due to the limited available data. However, it is not approved for COVID-19 patients aged 18 years and younger due to bone and cartilage growth and is not recommended for pregnant or breastfeeding women. In addition, molnupiravir is not authorized by the FDA for pre- or post-exposure prophylaxis for COVID-19. Due to its lack of clinical benefit, molnupiravir is not authorized for the treatment of hospitalized COVID-19 patients.[2]

In a one-to-one matched cohort study with molnupiravir by Butt et al.[12], 1459 patients were treated with molnupiravir in a study that included patients with COVID-19 for the first time. Molnupiravir use was not associated with a reduction in hospitalization and mortality within 30 days of COVID-19 diagnosis. The study reported that a group of patients who presented as asymptomatic benefited from molnupiravir.

Bernal et al.[13] included 1433 COVID-19 patients in their randomized, double-blind, placebo-controlled study with molnupiravir. Of the patients, 716 received molnupiravir treatment, and 717 received placebo treatment. In the study, the risk of hospitalization or death from any cause by day 29 was 7.3% (28 of 385 patients) with molnupiravir and 14.1% (53 of 377 patients) in the placebo group, with a statistically significant lower risk reported in the molnupiravir-treated group. One patient died on day 29 in the molnupiravir group, compared to nine deaths in the placebo group. In conclusion, early treatment with molnupiravir was reported to significantly reduce the risk of hospitalization or death in at-risk, unvaccinated adults with the COVID-19 infection.

Paxlovid (nirmatrelvir/ritonavir): Paxlovid is the first FDA-approved oral antiviral drug against COVID-19. It is a combination of nirmatrelvir, which inhibits the main protease (Mpro) of SARS-CoV-2, and ritonavir, a cytochrome P450-3A4 inhibitor, thereby slowing the metabolism of nirmatrelvir. This combination provides a longer effect. The half-life of nirmatrelvir allows a dosing interval of 12 hours. It is the first oral antiviral medicine approved for COVID-19. The FDA and the most recent guideline (NIH, IDSA, and NICE) versions recommend the use of Paxlovid in non-hospitalized adult and pediatric (≥12 years and ≥40 kg) patients with "mild to moderate COVID-19" to reduce the risk of disease progression.[2,11]

Side effects of Paxlovid include diarrhea, taste disturbance, hypertension, and myalgia. It is not recommended for patients with severe renal or hepatic impairment. It should be used with caution in patients with liver diseases, abnormal liver enzymes, or hepatitis. Use of Paxlovid in people with uncontrolled or undiagnosed HIV-1 infection may induce HIV-1 drug resistance. Paxlovid is contraindicated in patients with a history of clinically significant hypersensitivity reactions. Because it is a CYP-3A4 inhibitor, it is contraindicated in patients taking drugs metabolized by CYP-3A4, such as alfuzosin, colchicine, propafenone, amiodarone, ergotamine, statins, sildenafil, midazolam, and triazolam. Paxlovid dose should be adjusted in patients with eGFR≤60 mL/min. Paxlovid is not recommended for patients with an eGFR<30 ml/min.[2,9,11]

Lewnard et al.[14] investigated the efficacy of the drug in preventing hospital admissions and death in 7274 people who tested positive for SARS-CoV-2 who received nimatrelvir-ritonavir treatment and 126 152 people who did not receive treatment in a cohort study in the United States. In the study, 5,472 (75.2%) people receiving treatment and 84,657 (67.1%) people not receiving treatment were tested within 5 days of symptom onset. The study found that nirmatrelvir-ritonavir had an overall estimated effectiveness of 53.6% in preventing hospitalization or death within 30 days of a positive SARS-CoV-2 test, increasing to 79.6% when nimatrelvir-ritonavir was given within 5 days of symptom onset. In the subgroup of patients tested within 5 days of symptom onset and discontinued on the test day, the estimated efficacy of nimatrelvir-ritonavir was 89.6%. In conclusion, in a setting with high levels of COVID-19 vaccine uptake, nimatrelvir-ritonavir was reported to effectively reduce the risk of hospitalization or death within 30 days of a positive SARS-CoV-2 test in outpatients.

In a study conducted in the United States, nimatrelvir-ritonavir was reported to have greater efficacy in adults aged 65 years and older compared to adults aged 65 years and older. However, studies conducted in the United States and Hong Kong reported that efficacy did not differ according to age, immunity, or the presence of comorbidities.[14-16]

In a retrospective viral cohort study, the efficacy of nimatrelvir-ritonavir was investigated in outpatients with COVID-19, including BA.4 and BA.5, in Colorado, United States. The study found an association between nimatrelvir-ritonavir treatment and a reduction in all-cause 28-day hospitalization, all-cause mortality, and emergency department visits. The researchers reported that nirmatrelvir-ritonavir was effective in first-line treatment in adults with acute SARS-CoV-2 infection who were not hospitalized during an omicron period, including BA.4 and BA.5 sub-variants.[17]

Old Antiviral Drugs in COVID-19

Favipiravir: Like remdesivir, it is an RdRp inhibitor. It is a prodrug purine analogue, and its activated phosphoribosylated form (favipiravir-RTP) inhibits viral RNA polymerase activity and genome replication. Favipiravir was approved in Japan in 2014 for the treatment of influenza viruses. Due to the urgency of COVID-19, favipiravir was redesigned for the treatment of mild COVID-19 cases without

hospitalization and has been used off-label. However, NIH, IDSA, and NICE guidelines do not recommend or endorse the use of favipiravir for the treatment of COVID-19.

In vitro studies have revealed that favipiravir may be effective against SARS-CoV-2. However, there is controversy about its efficacy against COVID-19 in clinical trials. A meta-analysis showed that favipiravir reduced mortality by 30%, but this finding was not statistically significant. Clinical evidence supports the safety and tolerability of short-term use of favipiravir. The most commonly reported side effects of favipiravir are elevated liver transaminases, bilirubin, and uric acid, gastrointestinal disorders, chest pain, and teratogenicity; therefore, it is contraindicated in pregnancy.[2]

Shah et al.[18] compared the efficacy of favipiravir with standard therapy in the PIONEER open-label, phase 3 randomized controlled multicenter study. Of the 499 people included in the study, 251 received favipiravir and standard care, and 248 received standard care only. There was no significant difference between those who received favipiravir and standard care compared to those who received standard care only in the time to recovery in the overall study population. In post-hoc analyses, patients aged <60 years who received favipiravir and standard care showed a faster recovery rate compared to patients who received standard care only. Of the 251 patients who received favipiravir and standard care, 27 (11%) of 251 patients experienced 36 serious adverse events, compared to 33 serious adverse events in 27 (11%) of the 248 patients who received standard care only. These adverse events were reported as infectious, respiratory, and cardiovascular events in order of frequency. There was no significant difference between the groups in terms of serious adverse events per patient.

Favipiravir was found to be ineffective in the treatment of COVID-19 compared to standard treatment in randomized controlled trials and was largely withdrawn from use or replaced by more effective antiviral drugs.

Lopinavir/ritonavir: Lopinavir/ritonavir is a protease inhibitor approved by the FDA in 2000 for the treatment of HIV. Ritonavir is added because it is a cytochrome P450-3A4 inhibitor that slows the metabolism of lopinavir. This combination has been shown to inhibit SARS-CoV-1 and MERS-CoV replication in vitro and has been reported to reduce mortality due to ARDS in clinical trials. In an open-label, randomized, phase II study in the early phase of COVID-19, the triple combination of interferon beta-1b, ribavirin, and lopinavir/ritonavir was reported to shorten hospital stays in patients with mild to moderate COVID-19.[2,8]

Lopinavir/ritonavir did not show clinical efficacy in non-hospitalized COVID-19 patients in two randomized controlled trials. The NIH and IDSA do not recommend the use of lopinavir/ritonavir for the treatment of COVID-19 in hospitalized or non-hospitalized patients or for post-exposure prophylaxis. The most commonly reported side effects include nausea, vomiting, diarrhea, abdominal pain, loss of appetite, bloating, metallic taste, paresthesia, pruritus, prolonged QT interval, and hepatotoxicity, as well as drug interactions due to CYP3-A4 inhibitory activity.[2]

Evaluated the efficacy of nirmatrelvir-ritonavir and molnupiravir in outpatients when the Omicron variant was circulating. The study showed no difference in the risk of 30-day or 31 to 180-day hospitalization or death between matched participants treated with nirmatrelvir or molnupiravir. Nirmatrelvir-ritonavir was reported to be effective in reducing 30-day hospitalizations and deaths. Molnupiravir appeared to provide a benefit in terms of 30-day mortality but no benefit in hospitalization. No further reduction in mortality from 31 days to 180 days was observed with either antiviral.[20]

Pegylated Interferon Lambda

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes weak expression of type III interferons in infected cells, which are naturally produced as an early defense barrier line in upper respiratory tract infections. Interferon lambda, a type III interferon, is a member of a new cytokine family with antiviral effects that is highly similar to type I interferons (IFN-α and IFN-β).[21]

IFN λ (type 3 interferon) is secreted from virus-infected cells, macrophages, and dendritic cells. It stimulates antiviral activity in cells. Activates and regulates cellular components of innate immunity; initiates stimulation of the acquired immune response. It activates apoptosis-stimulating molecules and stimulates the progression of infected cells to apoptosis.[22]

Pegylated interferon lambda (PegIFN-lambda) has been applied in many clinical trials involving viral hepatitis agents and COVID-19 and has been shown to have a good safety and side effect profile. Pegylated interferon lambda has been shown to have broad-spectrum antiviral activity in multiple cell cultures, animal models, and clinical trials.

Reis et al.[22] investigated the effect of pegIFN-lambda on hospitalization within 28 days or observation longer than 6 hours in the emergency department (primary endpoint) in patients with acute COVID-19 in a prospective randomized controlled study. The study included 931 patients who received a single subcutaneous 180 µg pegIFN-lambda treatment and 1018 patients who received placebo treatment as a control group. The primary endpoint was 2.7% in the pegIFN lambda group and 5.6% in the control group. In the same study, the frequencies of hospitalization, death, and adverse events in the peg IFN lambda group and control groups were reported as 2.3%, 3.9%, 0.1%, 0.4%, 0.8%, and 1.1%, respectively. In conclusion, the researchers reported that hospitalization or emergency department visits (observation longer than 6 hours) in patients with mild to moderate COVID-19 were significantly reduced with a single dose of peg IFN lambda.

The main antiviral agents used in COVID-19 treatment, their mechanisms of action, adverse drug reactions, and drug interactions are summarized in the **Table 2**.

CONCLUSION

As a result of, although there are some antiviral drugs with proven efficacy in the treatment of COVID-19 in outpatients, we believe that antiviral drugs that are also effective against new variants of SARS-CoV-2, can be used in inpatients and prophylaxis, have a high resistance barrier, and have few side effects should be developed.

Table 2. Major antiviral agents used in the treatment of COVID-19, their mechanisms of action, adverse drug reactions, and drug interactions*

Antiviral medicine	Mechanism of action	Adverse drug reactions	Drug interactions
Remdesivir	RNA-dependent RNA polymerase inhibitor	Gastrointestinal disorders (nausea, vomiting), elevated transaminases, and infusion-related reactions (hypotension, diarrhea, tremor) Prolonged prothrombin time, hypersensitivity reaction	CYP3A4 enzyme stimulants reduce efficacy
Lopinavir-ritonavir (Kaletra)	3CL protease inhibitor, one of the main protease enzymes of SARS-CoV-2 virus	Gastrointestinal disorders (nausea, vomiting, diarrhea), elevated transaminases, increased bleeding, hyperlipidemia, hyperglycemia, insulin resistance, QT prolongation, risk of renal dysfunction	Inhibitor and substrate of CYP3A4 Substrate of CYP2D6
Favipiravir	RNA-dependent RNA polymerase inhibitor	Gastrointestinal disorders (nausea, vomiting, diarrhea), hyperuricemia, elevated transaminases, decreased neutrophil count	Inhibitor of CYP2C8, aldehyde oxidase and xanthine Enhances the toxic effects of pyrazinamide
Molnupiravir	Molnupiravir increases the frequency of viral RNA mutations in human and animal models and disrupts SARS-CoV-2 replication.	Nausea, diarrhea, and dizziness. Contraindicated in pregnant and lactating women and under 18 years of age.	No drug interactions have been reported so far
Nirmatrelvir-ritonavir	Nirmatrelvir inhibits the main protease (Mpro) of SARS-CoV-2, ritonavir is a P4503A4 inhibitor, slowing the metabolism of nirmatrelvir.	Diarrhea, taste disturbance, hypertension, and myalgia. Not recommended in severe hepatic and renal failure. It should be used with caution in patients with liver disease, hepatitis, and elevated liver enzymes. Use in patients with HIV-1 infection may induce HIV-1 antiviral resistance.	It is a CYP-3A4 inhibitor. Contraindicated in patients taking drugs metabolized by CYP-3A4 such as colchicine, propafenone, amiodarone, ergotamine, statins, sildenafil, midazolam, triazolam

(*) Part of references 2,23,24 is cited

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Tanriverdi ES, Yakupoğulları Y, Otlu B. COVID-19 etkeninin özellikleri. In: Çiçek C, editör. Mikrobiyoloji ve COVID-19. Türkiye Klinikleri: 2020:7-14.
2. Aboul-Fotouh S, Mahmoud AN, Elnahas EM, Habib MZ, Abdelraouf SM. What are the current anti-COVID-19 drugs? From traditional to smart molecular mechanisms. *Virol J.* 2023;20(1):241. doi: 10.1186/s12985-023-02210-z
3. Çınar G, Birengel S. Remdesivir. In: Birengel S, Balık İ, eds. COVID-19 Tedavi Uygulamaları: Kanıt Değerleri. Türkiye Klinikleri: 2021:11-14.
4. World Health Organization, WHO Coronavirus Disease (COVID-19). woldometers.info/coronavirus
5. T.C. Sağlık Bakanlığı COVID-19 aşısı bilgilendirme platformu. https://covid19asi.saglik.gov.tr/
6. Cesur S, Özsoy M. Antiviral ilaçlar [Lopinavir/ ritonavir ve diğer proteaz inhibitörleri (Darunavir-kobisistat), ribavirin, diğer antiviraller: Arbidol (Umifenovir), camostat]. In: Birengel S, Balık İ, eds. COVID-19 Tedavi Uygulamaları: Kanıt Değerleri. Türkiye Klinikleri: 2021:15-19.
7. Yalçı A. Antiparaziter ve antibakteriyel ilaçlar (Klorokin, hidroksiklorokin, nitazoksanid, ivermektin, azitromisin). In: Birengel S, Balık İ, eds. COVID-19 Tedavi Uygulamaları: Kanıt Değerleri. Türkiye Klinikleri: 2021:1-5.
8. Yuan Y, Jiao B, Qu L, Yang D, Liu R. The development of COVID-19 treatment. *Front Immunol.* 2023;14:1125246. doi: 10.3389/fimmu.2023.1125246
9. National Institutes Health (NIH). COVID-19 Treatment Guidelines. https://files. covid19treatment guidelines.nih.gov/guidelines/section/section_38.pdf Updated November 2, 2023
10. Strizki JM, Gaspar JM, Howe JA, et al. Molnupiravir maintains antiviral activity against SARS-CoV-2 variants and exhibits a high barrier to the development of resistance. *Antimicrob Agents Chemother.* 2024;68(1):e00953-23. doi: 10.1128/aac.00953-23
11. Alpizar SA, Accini J, Anderson DC, et al. Molnupiravir for intra-household prevention of COVID-19: the MOVe-AHEAD randomized, placebo-controlled trial. *J Infect.* 2023;87(5):392-402.
12. Butt AA, Yan P, Shaikh OS, Omer SB, Mayr FB, Talisa VB. molnupiravir use and 30-day hospitalizations or death in a previously uninfected nonhospitalized high-risk population with COVID-19. *J Infect Dis.* 2023;228(8):1033-1041.
13. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med.* 2022;386(6):509-520. doi: 10.1056/NEJMoa2116044
14. Dryden-Peterson S, Kim A, Kim AY, et al. Nirmatrelvir plus ritonavir for early COVID-19 in a large US health system: a population-based cohort study. *Ann Intern Med.* 2023;176(1):77-84.
15. Yip TCF, Lui GCY, Lai MSM, et al. Impact of the use of oral antiviral agents on the risk of hospitalization in community COVID-19 patients. *Clin Infect Dis.* 2022;76:e26-e33.
16. Shah MM, Joyce B, Plumb ID, et al. Paxlovid associated with decreased hospitalization rate among adults with COVID-19—United States, April–September, 2022. *MMWR Morb Mortal Wkly Rep.* 2022;71(48):1531-1537.
17. Aggarwal NR, Molina KC, Beaty LE, et al. Real-world use of nirmatrelvir-ritonavir in outpatients with COVID-19 during the era of omicron variants including BA.4 and BA.5 in Colorado, USA: a retrospective cohort study. *Lancet Infect Dis.* 2023;23(6):696-705. doi:10.1016/S1473-3099(23)00011-7
18. Shah PL, Orton CM, Grinsztejn B, et al. Favipiravir in patients hospitalised with COVID-19 (PIONEER trial): a multicentre, open-label, phase 3, randomised controlled trial of early intervention versus standard care. *Lancet Respir Med.* 2023;11(5):415-424.
19. Bajema KL, Berry K, Streja E, et al. Effectiveness of COVID-19 treatment with nirmatrelvir-ritonavir or molnupiravir among US veterans: target trial emulation studies with one-month and six-month outcomes. *Ann Intern Med.* 2023;176(6):807-816. doi: 10.7326/M22-3565
20. Lasfar A, Zloza A, Silk AW, Lee LY, Cohen-Solal KA. Interferon lambda: toward a dual role in cancer. *J Interferon Cytokine Res.* 2019;39(1):22-29. doi: 10.1089/jir.2018.0046
21. Heim MH, Thimme R. Innate and adaptive immune responses in HCV infections. *J Hepatol.* 2014;61(1):S14-S25.
22. Reis G, Moreira Silva EAS, Medeiros Silva DC, et al. Early treatment with pegylated interferon lambda for COVID-19. *N Engl J Med.* 2023;388(6):518-528.
23. Lam S, Lombardi A, Ouanounou A. COVID-19: a review of the proposed pharmacological treatments. *Eur J Pharmacol.* 2020;886:173451. doi: 10.1016/j.ejphar.2020.173451
24. Kabinger F, Stiller C, Schmitzová J, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nat Struct Mol Biol.* 2021;28(9):740-746. doi: 10.1038/s41594-021-00651-0