Antiviral Treatment in COVID-19 Outpatients: A Systematic Review of Randomized Controlled Trials

David Setyo Budi[1], Puguh Oktavian[1], Tri Pudy Asmarawati[2], Pudji Lestari[3]*, Fauziah Ariviani[1], Raka Ihsanulhaj[1], Tamara Tsania[1], Danise Febiola[1], Naomi Lesmana Putri[1]

[1]Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Internal Medicine, Faculty of Medicine Universitas Airlangga - Universitas Airlangga Hospital, Surabaya, Indonesia.
[3]Department of Public Health, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia.

**** Corresponding Author:***
Pudji Lestari, MD. Department of Public Health, Faculty of Medicine Universitas Airlangga. Jl. Mayjen Prof. Dr. Moestopo 47, Surabaya 60131, Indonesia. Email: pudjilestari70@fk.unair.ac.id.

ABSTRACTS

Background: *Most COVID-19 patients have mild or moderate illnesses that can progress to severe illness, leading to hospitalization and/or mortality. The use of antivirals to prevent the progression of COVID-19 in non-hospitalized patients shows conflicting result and efficacy remain unclear. This study evaluates the efficacy and safety of antivirals therapy in COVID-19 outpatients.* ***Methods:*** *Search were conducted in Pubmed, ScienceDirect, Cochrane Library, Springer, medRxiv, Journal Storage [JSTOR], and Directory of Open Access Journals [DOAJ] for articles investigating antivirals in COVID-19 outpatients. In addition, clinical and virological outcomes, COVID-19 hospitalization, all caused mortality, and adverse events were assessed.* ***Results:*** *Thirteen studies were included in this review. The consecutive data from these studies suggested that favipiravir is more optimally used in early disease, but improvement in symptoms shows inconsistent results. Meanwhile, molnupiravir shows consistent results, which can reduce hospitalization and mortality risk. In addition, remdesivir and nirmatrelvir-ritonavir have the potential to prevent the progression of COVID-19 in outpatients, but the data provided in this study are very limited. Finally, there is no significant difference in serious and non-serious adverse events, highlighting that antivirals have a good safety profile.* ***Conclusion:*** *This study provides an overview of the role of various antivirals therapy in COVID-19 outpatients. Molnupiravir, remdesivir, and nirmatrelvir-ritonavir have shown potential to prevent the progression of COVID-19 in early disease. However, this review was based on very limited data. Therefore, further clinical trials are needed to confirm this finding.*

Keywords*: COVID-19, SARS-COV-2, antiviral, outpatients, systematic review.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization on March 11th, 2020.[1] As of March 2nd, 2022, there were 437 million confirmed cases and 5.9 million deaths were caused by COVID-19 worldwide.[2] The clinical manifestation of COVID-19 can range from asymptomatic status, acute respiratory disease, and pneumonia, to acute respiratory distress syndrome. One of the factors of disease progression of COVID-19 are comorbidities such as chronic hypertension, organ damage, and coagulation dysfunction.[3] Currently, therapy is used based on the severity of COVID-19. In hospitalized COVID-19, corticosteroids and antivirals are recommended

for severe COVID-19. In addition, the majority of the patients were classified as mild or moderate illnesses with some of them progressing into severe illness and needing hospitalization.[4] Because of that, prevention of illness progression in an outpatient setting is important to decrease the risk of death and healthcare workload.

The choice of treatment for outpatient COVID-19 patients is still a matter of debate. Neutralizing antibody exhibits a significant antiviral effect when administered early in COVID-19 outpatients. However, the presence of the SARS-CoV-2 variant may escape the neutralizing antibody response.[5] Even so, antivirals are one of the treatment options in COVID-19 outpatients since they are not affected by spike-protein variants. Several antivirals have been used in clinical trials by COVID-19 outpatients, including remdesivir, favipiravir, tenofovir disoproxil fumarate, and molnupiravir which are antivirals groups that inhibit RNA synthesis.[6,7] The active form of these drugs will act on the RdRp enzyme and can interfere with the transcription process. RdRp is an enzyme that works on the viral genome (+gRNA) and will form a complementary strand (-gRNA) through the transcription process, so it will be able to kill the virus via chain termination and mutagenesis.[8] In addition, protease inhibitors such as nirmatrelvir, lopinavir, and ritonavir can inhibit the translation of polypeptides into protein components by inhibiting 3-chymotrypsin-like protease (3CLpro). This enzyme plays a role in the viral life cycle by breaking down polyproteins (PP1A and PP1AB) into functional viral proteins.[6,9,10] Then there is umifenovir, a drug with a mechanism of action targeting spike protein, angiotensin-converting enzyme 2 (ACE2), and inhibiting viral envelope membrane fusion[11]. Moreover, there are sofosbuvir and daclatasvir which are NS5B polymerase inhibitors and NS5A inhibitors that can inhibit the viral replication process.[12]

Studies on the use of antivirals in COVID-19 outpatients are still scarce. According to its capability, antivirals can potentially prevent worsening of clinical manifestation especially when given earlier in the disease manifestation. Several randomized controlled trials (RCTs) on antiviral therapy in COVID-19 outpatients have recently been published and produced conflicting results. Therefore, in this systematic review, we aim to comprehensively evaluate the efficacy and safety of antivirals therapy in COVID-19 outpatients. The parameters of efficacy were assessed based on clinical outcomes such as WHO average score, time to alleviation of symptoms, and COVID-19 related symptoms. Meanwhile, safety is assessed from non-serious adverse event and a serious adverse event. Non-serious adverse events is defined as any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of an investigational product serious adverse events are defined as events that, at any dose, result in the following: death, life-threatening, in-patient hospitalization or prolongation of existing hospitalization, and persistent or significant disability.

METHODS

This systematic review and meta-analysis are written based on the 2020 guideline for Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA),[13] and registered in the database for PROSPERO (CRD42022313970).

Eligibility Criteria

This study used randomized controlled trials (RCTs) as the required type of study. Two authors (DSB and PO) scanned through the titles and abstracts for each journal based on the eligibility criteria as follows: (1) COVID-19 outpatients; (2) studies involving antiviral therapy; (3) reported at least one of the outcomes of interest (4) English language literature. The primary outcomes included clinical recovery, the need for hospitalization, and adverse events with the secondary outcomes being laboratory outcomes. Reviewed articles, non-human studies, irrelevant articles, and duplicates are excluded.

Search Strategy and Selection of Studies

Two authors (PO and FA) have been conducting keyword searches on September 10th, 2021 for related materials published in databases (Pubmed, ScienceDirect, Cochrane Library, Springer, Journal Storage [JSTOR], and Directory of Open Access Journals

[DOAJ]). The following keywords were used: "((Covid) OR (SARS-COV-2)) AND ((Antiviral) OR (Remdesivir) OR (Molnupiravir) OR (Favipiravir) OR (Nirmatrelvir)) AND ((Outpatient) OR (Non-hospitalized))". We also performed manual searches, extended from September 11th, 2021 to March 10th, 2022. Additional details about the search strategy can be found in ***Supplementary Materials***. Titles and abstracts were screened individually from every article gathered until this point to identify potentially eligible studies, to then having full text screening. Any disagreements between these two authors were resolved by discussion with all authors until consensus was reached.

Data Extraction

Relevant data were independently extracted using a structured and standardized format from each study selected by two authors (DSB and PO). The following information was extracted: first author name and year of publication, study design, country of origin, sample size, patient age, disease severity, antivirals dose and duration, combination therapy and outcomes (clinical outcome, laboratory outcome, and adverse events).

Quality Assessment

The methodological quality of each study was assessed independently by two authors (DSB and PO) using the Cochrane Risk of Bias Tool for Randomized Trials (RoB ver.2).[14] Studies were classified as "low risk of bias", "some concerns" or "high risk of bias".

Statistical Analysis

Considering the important differences in the comparison of each study and various outcome measures, we could not generate meta-analyses of the included studies; instead, we narratively synthesized the evidence.

RESULTS

Study Selection

From the database and manual research, we acquired 5946 and 125 records, respectively. After a screening process of titles and abstracts, 36 potentially eligible articles were selected for review. After a full-text assessment, 13 studies were included for a systematic review. The study selection process is summarized in the PRISMA flow chart **(Figure 1).**

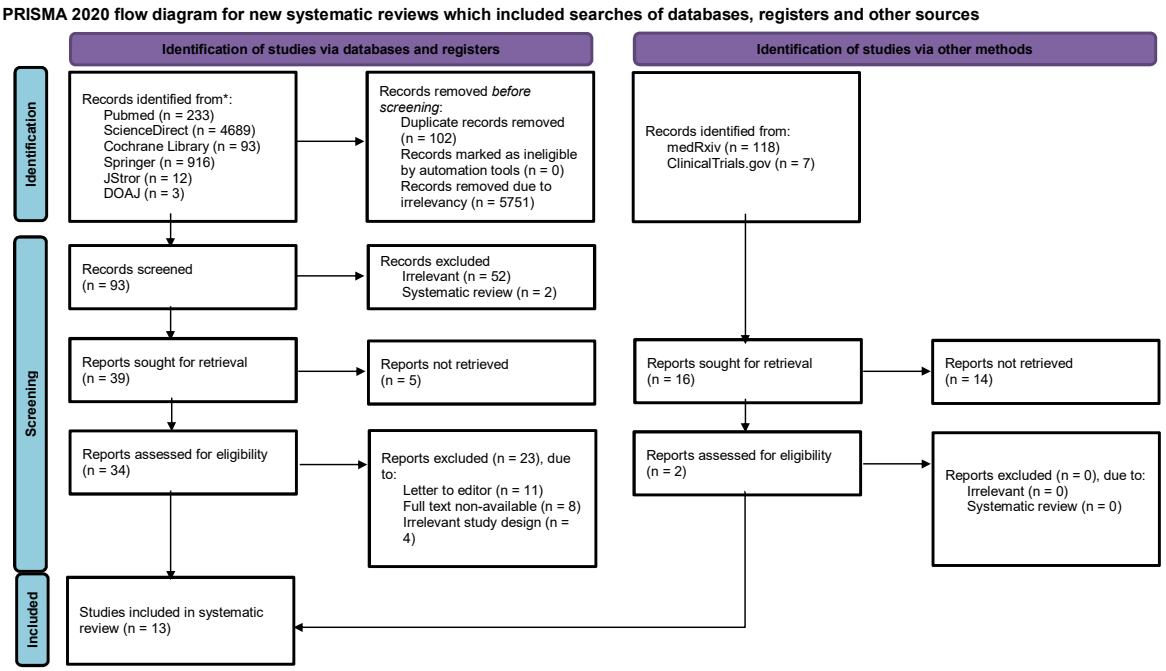

Figure 1. PRISMA flow chart.

Quality Assessment

Ten RCTs[15–24] were considered to be low-risk of bias studies and three RCTs[25–27] have some concerns according to Cochrane's Risk of Bias 2 (RoB2) assessment. In addition, details of the quality of assessment are summarized in ***Supplementary Materials*. (Table S2)**

Study Characteristics

Thirteen studies were found with a total of 3078 COVID-19 outpatients belonging to the antivirals therapy group and 2839 patients belonging to the placebo or standard therapy as a control group. In this review, all studies are RCTs conducted in the United States, France, Iran, and multiple countries, including several centers in various countries. In this review, there are several antivirals used including favipiravir,[15–17,25] molnupiravir,[18,19,26] remdesivir,[20] tenofovir disoproxil fumarate,[27] nirmatrelvir-ritonavir,[21] lopinavir-ritonavir,[22] umifenovir,[23] sofosbuvir-daclatasvir.[24] Meanwhile, standard therapy consisted of hydroxychloroquine, corticosteroid, antibiotics (such as azithromycin), and vitamin supplements.[23–26] In clinical outcomes, several criteria are used, such as WHO average score, time to alleviation of symptoms, and COVID-19 related symptoms. The eight-category ordinal scale defined by WHO consists of the following categories: no clinical or virological evidence of infection (score = 0), no limitation of activities (score = 1), limitation of activities (score = 2), hospitalized, no oxygen therapy (score = 3), oxygen by mask or nasal prongs (score = 4), non-invasive ventilation or high flow oxygen (score = 5), intubation and mechanical ventilation (score = 6), ventilation support, PRC, ECMO (score = 7), and death (score = 8).[23] The characteristics and outcomes summary for each study is presented in **Table 1** and **Table 2.**

Patients Characteristics

The mean patient age was 45 ± 10 years. Regarding disease severity, 61.6% of the outpatients were mild, and 38.4% were moderate.[15–27] Meanwhile, 6 studies consisted of a high-risk population that had comorbidities such as age >60 years old; active cancer; chronic kidney disease; chronic obstructive pulmonary disease; pulmonary hypertension; obesity; severe heart conditions; diabetes mellitus; history of transplantation; immunocompromised status due to disease or medication.[16,18–22] While 7 studies consisted of low-risk populations in which comorbid factors were excluded.[15,17,23–27] In addition, 6 studies are reporting on the vaccination status of which 4 studies used the unvaccinated population,[16,18,19,21] while 1 study used the vaccinated population where at least 1 dose of vaccine was used,[20] and 1 study used both vaccinated and unvaccinated populations.[17]

Clinical Outcomes

Seven studies report clinical outcomes with different parameters, such as time to alleviation of symptoms, WHO average score, and COVID-19 related symptoms.[15,16,20,23–25,27] The use of favipiravir reported no significant difference in median time to alleviation of symptoms between favipiravir versus placebo in the study conducted by Bosaeed et al., 2022 (7 days [IQR: 4-11] vs 7 days [IQR: 5-10]], p=0.51),[15] and Holubar et al., 2021 (15 days [IQR: 12-26] vs. 14 days [IQR: 11-18], p=0.43).[16] Meanwhile, Ruzhentsova et al., 2021 reported significant results regarding the median time to alleviation of symptoms between favipiravir compared with standard therapy (6.0 days [IQR: 4.0-12] vs 14 days [IQR: 5.0-12], p=0.019).[25] The remdesivir as an intervention of antivirals therapy reported an alleviation of symptoms on day 14 between the remdesivir group versus the placebo group of 23/66 patients (34.8%) vs 15/60 (25.0%), rate ratio of 1.41; 95% CI 0.73 to 2.69.[20] Meanwhile, the combined use of tenofovir disproxil fumarate plus emtricitabine did not show a greater improvement in COVID-19 symptoms compared to standard therapy (6/30 (20%) vs 3/30 (10%), p=0.29).[27] Meanwhile, the use of sofosbuvir plus daclatasvir also did not show significant results in terms of reducing the symptoms of COVID-19 on day 5 compared to standard therapy (12/27 patients (44%) vs. 12/28 (43%), p= 1.00).[24] In addition, umifenovir showed a difference in the mean WHO score compared to placebo in the Mild-asymptomatic group on day 5 (0.45 ± 0.11 vs. 0.88 ± 0.13, p= 0.019). These results contrast the moderate population where umifenovir compared with

Table 1. Characteristics of the included studies.

References	Study design	Country	Sample size		Age, years Mean ± SD/Median (IQR)		Disease severity	Dosage and administration	
			Intervention (n)	Control (n)	Intervention	Control		Intervention	Control
Bosaeed et al., 2022[15]	RCT	Saudi Arabia	112	119	37 [31.5-45]	36 [32-44]	Low risk, non-hospitalised, mild illness	Oral favipiravir 1800mg twice daily on day 1 followed by 800mg twice daily for a total duration of 5 to 7 days therapy	Placebo
Holubar et al., 2021[16]	RCT	United States	75	74	42.5 ± 12	42.8 ± 12	Unvaccinated, low risk non-hospitalised, mild illness	Oral favipiravir 1800mg twice daily on day 1 followed by 800mg twice daily for a total duration of 10 days therapy	Placebo
Lowe et al., 2022[17]	RCT	United Kingdom	180 (favipiravir+lopinavir-ritonavir= 61 Favipiravir =59 Lopinavir-ritonavir= 60)	60	Favipiravir++lopinavir-ritonavir= 40.3 ±13.1 favipiravir= 40.3 ±12.1 lopinavir-ritonavir= 38.6 ±11.5	40.6 ±12.2	Both vaccinated and unvaccinated, low risk, non-hospitalised, mild illness	Oral favipiravir 800 mg twice daily on Day 1, followed by 400 mg four times daily from day 2 to day 7 Oral lopinavir-ritonavir 400mg/100 mg twice daily on day 1, followed by 200mg/50mg four times daily from day 2 to day 7 Oral favipiravir (1800mg twice daily on day 1 followed by 400mg four times daily on days 2-7) PLUS lopinavir-ritonavir (400mg/100mg twice daily on day 1, followed by 200mg/50mg four times daily on days 2-7)	Placebo
Bernal et al., 2021[18]	RCT	Multiple countries	716	717	44 ± 15	45 ± 15	Unvaccinated adult, High risk non-hospitalised, mild to moderate illness	Oral molnupiravir 800 mg for 5 days twice daily	Placebo

Fischer et al., 2022[19]	RCT	United States	140 : 23=200mg 62=400mg 55=800mg	62	200 mg: 34.76 ± 11.92 400 mg: 43.73 ± 13.55 800 mg: 42.17 ± 10.97	Median age (range): 39 (19-71) 39.92 ± 11,18	Unvaccinated adult, high risk non-hospitalised, mild to moderate illness	Oral molnupiravir 200 mg, 400 mg, and 800 mg for 5 days twice daily	Placebo
Gottlieb et al, 2022[20]	RCT	United States, Spain, Denmark, United Kingdom	279	283	50 ± 15	51 ± 15	Vaccinated, High-risk non-hospitalized, mild to moderate illness	IV remdesivir (200 mg on day 1, 100 mg on days 2 and 3)	Placebo
Hammond et al., 2022[21]	RCT	Multiple countries	1120	1126	45 ± 10	46 ± 10	Unvaccinated adult, High risk, non-hospitalised, mild to moderate illness	Oral nirmatrelvir (300 mg) + Ritonavir (100 mg) for 5 days twice daily	Placebo
Reis et al., 2021[22]	RCT	Brazil	244	227	54 [18-94]	53 [18-80]	high-risk, non-hospitalized, mild to moderate illness	Oral lopinavir-ritonavir loading dose of 800 mg and 200 mg, respectively, every 12 hours in day 1, followed by 400 mg and 100 mg, respectively, every 12 hours for the next 9 days	Placebo
Ramachandran et al., 2022[23]	RCT	India	60	63	46.08 ± 1.93	47.35 ± 1.96	Low risk, non-hospitalised, mild to moderate illness	Oral umifenovir 800 mg for 14 days twice daily + Standard of care	Standard of care
Roozbeh et al., 2020[24]	RCT	Iran	27	28	43.3 ± 3.7	46.8 ± 3.9	low risk non hospitalized, mild to moderate illness	Oral sofosbuvir (400 mg) + daclatasvir (60 mg) + hydroxychloroquine (200 mg) for 7 days twice daily	Standard therapy
Ruzhentsova et al.2021[25]	RCT	Russia	83	44	41,7 ± 10,6	42,0 ± 10,4	low risk non hospitalized, mild to moderate illness	Oral favipiravir loading dose 1800 mg BID on day 1, followed by 800 mg BID on days 2-10	Standard of care

Khoo et al., 2021[26]	RCT	United Kingdom	12 Molnupiravir (300 mg, N=4; 600mg, N=4; 800 mg, N=4)	6	300 mg: 56.0[51.0-80] 600 mg: 43 [22-60] 800 mg: 39[25-63]	Median age of Standard of care (range): 59.0 (22.0-63.0)	Non hospitalized, asymptomatic, mild illness	Oral molnupiravir 300 mg, 600 mg, and 800 mg twice daily	Standard of care
Parienti et al.,2021[27]	RCT	France	30	30	39.9 ± 14.8	42.6 ± 16.7	low risk non hospitalized, mild to moderate illness	Oral single tablet of 245 mg tenofovir disoproxil fumarate + 200 mg emtricitabine (2 tablets on day 1, 1 tablet on days 2-7)	Standard of care

SD, standard deviation; IV, intravenous; NA, not available

Table 2. Data extraction for each individual studies.

Reference	Clinical outcomes		Covid-19 related hospitalization N (%)		Mortality N (%)		Laboratory parameters (Mean ± SD / Median)		Adverse events N (%)	
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Bosaeed et al., 2022[15]	Time to Alleviation of Symptoms (Median) : 7 days (IQR: 4-11)	Time to Alleviation of Symptoms (Median) : 7 days (IQR: 5-10)	6/112 (5.3%)	2/119 (1.6%)	0/112 (0%)	0/119 (0%)	Viral clearance within 15 days: 42/112 (37.5%)	Viral clearance within 15 days: 49/119 (41.1%)	Any AE: 8/112 (7.1%)	Any AE: 7/119 (5.8%)
Holubar et al., 2021[16]	Time to Alleviation of Symptoms (Median) : 15 [12-26]	Time to Alleviation of Symptoms (Median) : 14 [11-18]	0/75 (0%)	4/74 (5%)	0/75	0/74	Viral clearance at day 7: 10/42 (24%)	Viral clearance at day 7: 10/47 (21%)	Any AE: 19/75 (25.3) Serious AE: 0/75	Any AE: 10/74 (13.5) Serious AE: 1/74
Lowe et al., 2022[17]	NA	NA	NA	NA	0	0	Viral clearance at day 5 favipiravir: 25 (46.3%)* lopinavir-ritonavir: 17 (30.4%) favipiravir + lopinavir-ritonavir: 20 (35.7%)	Viral clearance at day 5 : 14 (26.9%)	Any AE: favipiravir: 38 (64.4) lopinavir-ritonavir: 59 (98.3)* favipiravir + lopinavir-ritonavir: 55 (90.1)	Any AE: 39 (65.0)
Bernal et al., 2021[18]	NA	NA	28/385 (7.3%)	53/377 (14.1%)	1 (0.1%)*	9 (1.3%)	Change of viral load: at days 3= -1.08±1.287* at days 5= -2.09 ±1.49*	Change of viral load: at days 3= -0.84±1.258 at days 5= -1.79±1.513	Any AE= 216 (30.4%) Serious AE=49 (6.9%)	Any AE= 231 (33.0%) Serious AE= 67 (9.6%)

Fischer et al., 2022[19]	NA	NA	NA	NA	NA	NA	Change of viral load: day 5 200 mg: -1.471 (0.212) 400 mg: -1.754 (0.128)* 800 mg: -1.867 (0.126)* Positive Covid-19 at day 5= 200mg:1/22(4.5) 400mg: 0/42* 800mg: 0/53*	Change of viral load: Day 5: -1.320 (0.150) Positive Covid-19 at day 5= 6/54(11.1)	Any AE: Pooled: Any AE of 200 mg = 11 (47.8) Any AE of 400 mg = 20 (32.3) Any AE of 800 mg = 11 (20.0) Any Serious AE of 200 mg = 0 Any Serious AE of 400 mg = 2 (3.2) Any Serious AE of 800 mg = 1 (1.8)	Any AE = 18 (29.0) Any Serious AE = 1 (1.6)
Gottlieb et al, 2022[20]	FLU-PRO Plus questionnaire: 61/169 (36.1%) reported improvement in symptoms on day 14	FLU-PRO Plus questionnaire: 33/165 (20.0%) reported improvement in symptoms on day 14	2/279 (0.7%)*	15/283 (5.3%)	0/279 (0%)	0/283 (0%)	Change of viral load at day 7: 6.31±1.75 to 4.11±1.36 = −1.24 log10 copies per milliliter	Change of viral load at day 7: 6.28±1.79 to 4.06±1.19 = −1.14 log10 copies per milliliter	Any AE: 118 (42.3%) Serious AE: 5 (1.8)	Any AE: 131 (46.3%) Serious AE: 19 (6.7)
Hammond et al., 2022[21]	NA	NA	8/1039 (0.77%)*	65/1046 (6.31%)	0/1039 (0%)*	12/1046 (1.15%)	NA	NA	Any AE = 251 (22.6%) Serious AE = 18 (1.6%)	Any AE= 266(23.9%) Serious AE= 74(6.6%)
Reis et al., 2021[22]	NA	NA	14/244 (5.7%)	11/227 (4.8%)	2/244 (0.8%)	1/227 (0.4%)	viral clearance: 125/201 (62.2%)	viral clearance: 112/195 (57.4%)	Serious AE: 20/232 (8.6%)	Serious AE: 12/220 (5.5%)
Ramachandran et al., 2022[23]	Average WHO scores for Mild-asymptomatic group at day 5: 0.45 ± 0.11* for Moderate group at day 5: 1.60 ± 0.32	Average WHO scores for Mild-asymptomatic group at day 5: 0.88 ± 0.13 for Moderate group at day 5: 1.95 ± 0.32	NA	NA	0 (0)	0 (0)	Viral clearance of mild-asymptomatic patients at day 5: 29/40(73%)*	Viral clearance of mild-asymptomatic patients at day 5: 17/42 (40%)	Any AE = 7 (11.7%)	Any AE = 7 (11.1%)

Roozbeh et al., 2020[24]	COVID-19 related symptoms: day 5 = 12/27 (44%) day 7= 7/27 (26%)	COVID-19 related symptoms: day 5 = 12/28 (43%) day 7= 7/28 (28%)	1 (4%)	4 (14%)	NA	NA	NA	NA	NA	NA
Ruzhentsova et al., 2021[25]	Time to Alleviation of Symptoms (Median) : 6.0 [4.0-12]*	Time to Alleviation of Symptoms (Mean ± SD / Median) : 14 [5.0-12]	3/112 (3.6%)	2/56 (4.5%)	NA	NA	Rate of viral clearance: day 3=80/112 (71.4%)* day5=91/112 (81.2%)*	Rate of viral clearance: day 3=32/56 (57.1%) day5=38/56 (67.9%)	Any AE: 80 (74.1%) Serious AE=2 (1.9%)	Any AE: 33 (60.0%) Serious AE: 0 (0%)
Khoo et al., 2021[26]	NA	NA	NA	NA	NA	NA	NA	NA	Any AE: 300 mg = 4 (100.0) 600 mg = 4 (100.0) 800 mg = 1 (25.0)	Any AE: 5 (83.3)
Parienti et al.,2021[27]	symptoms related to COVID-19 at day 7: 6/30 (20%)	symptoms related to COVID-19 at day 7: 3/30 (10%)	NA	NA	0 (0%)	0 (0%)	NA	NA	Serious AE: 2 (6%)	Serious AE: 1 (3%)

NR, not reported; SD, standard deviation; NA, not available; AE, adverse events* $p<0.05$ ** $p<0.001$

placebo did not show significant results (1.60 ± 0.32 vs. 1.95 ± 0.32, p = 0.281).[23]

COVID-19 Related Hospitalization

Eight studies reported hospitalization that was correlated with COVID-19.[15,16,18,20–22,24,25] Three RCTs using favipiravir conducted by Bosaeed et al., 2022, Holubar et al., 2021 and Ruzhentsova et al., 2021 have consistently shown that the favipiravir group did not reduce the risk of COVID-19 related hospitalization when compared to the control group (6/ 112 (5.3%) vs 2/119 (1.6%), p= 0.16), (0/75 (0%) vs 4/74 (5%), p= 0.06), (3/112 (3.6%) vs 2/56 (4.5%), p=0.494), respectively.[15,16,25] Meanwhile, lopinavir-ritonavir also did not show any difference in terms of hospitalization compared to placebo (14/244 (5.7%) vs 11/227 (4.8%, p>0.05).[22] Sofusbufir plus daclatasvir therapy reported that 1/27 (4%) patients needed hospitalization, which was not significantly different from the standard therapy group 4/28 (14%) (p=0.352).[24] Remdesivir showed a lower risk of COVID-19 related hospitalization by 87% in the remdesivir group compared to placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.03 to 0.59; P = 0.008).[20] Meanwhile, the combination of nirmatrelvir plus ritonavir showed lower hospitalizations rate compared to placebo (8/1039 (0.77%) vs. 65/1046 (6.31%), p<0.001).[21] In addition, molnupiravir showed a lower mean hospitalized or death rate than placebo at day 29 (7.3% [28 of 385 participants vs 14.1% [53 of 377 participants, a treatment difference of 6.8 percentage points (95% confidence interval [CI], 11.3 to 2.4; P = 0.001).[18]

Mortality

Three studies are reporting all-cause mortality outcomes.[18,21,22] Bernal et al., 2022 reported one death in the molnupiravir group and nine deaths in the placebo group on day 29. The risk of all caused mortality was lower by 89% (95% CI, 14 to 99) with molnupiravir than with placebo.[18] Meanwhile, nirmatrelvir plus ritonavir showed lower mortality in that there were 0 out of 1039 participant deaths in the intervention group compared to 12 out of 1046 participant deaths in placebo (p < 0.001).[21] Meanwhile, Lopinavir-ritonavir did not show any significant difference when compared with placebo (2/244 (0.8%) vs. 1/227 (0.4%), p>0.05).[22]

Laboratory Parameters

Nine studies reported laboratory outcomes including rate and time of viral clearance, and change of viral load.[15–20,22–25] Giving favipiravir can increase the rate of viral clearance significantly compared to the standard therapy group on day three and day five (80/112 (71.4%) vs. 32/56 (57.1%), p=0.03) and (91/112 (81.2%) vs 38/56 (67.9%), p=0.022), respectively.[25] Meanwhile, on day 7, the rate of viral clearance did not show any difference between the favipiravir group compared to standard therapy (95 (84.8%) vs 46 (82.1%), p=0.296).[25] In addition, Bosaeed et al., 2022 reported that the rate of viral clearance at day 15 also showed no significant difference between recipient favipiravir versus placebo (42/112 (37.5%) vs. 49/119 (41.1%), p>0.05).[15] Meanwhile, giving favipiravir showed a significant viral clearance at day 5 compared to control group (25 (46.3%) vs. 14 (26.9%), p=0.03).[17] Next, Holubar et al., 2021 reported no significant viral clearance between the favipiravir group versus control group on day 7 (10/42 (24%) vs 10/47 (21%), p=0.80).[16] Administration of molnupiravir was associated with greater reductions from baseline in mean viral load than the control group on day 3 (-1.08±1.287 vs -0.84±1.258) and day 5 (-2.09 ±1.490 vs -1.79±1.513).[18] Furthermore, Fischer et al., 2022 reported that at 400 mg and 800 mg doses of molnupiravir, the least-squares mean viral load change from baseline was significantly greater at day 5 than in the placebo group, with differences of -0.434log10 copies/ml (p =0.030) and 0.547log10 copies/ml (p=0.006), respectively.[19] In addition, administration of 400 mg and 800 mg of molnupiravir significantly increased viral clearance at day five compared to placebo (0/42 (0.0) vs 6/54 (11.1), p= 0.034) and (0/53 (0.0)) vs. 6/54 (11.1), p=0.003).[19] Meanwhile, the administration of remdesivir showed no difference in the least-squares mean viral load change from baseline on day 7 compared to placebo administration, with differences (-1.24 log10 copies per milliliter vs -1.14 log10 copies per milliliter, p=0.07).[20]

Administrations of lopinavir plus ritonavir (OR, 1.04; 95% CI, 0.94-1.16) showed no difference in viral clearance compared to placebo.[22] In mild-asymptomatic patients receiving umifenovir showed greater viral clearance than standard therapy on day 5 (29/40(73%) vs 17/42 (40%), p=0.002).[23]

Adverse Events

Non-serious Adverse Events

Ten studies reported minor adverse events after receiving antiviral therapy.[15–21,23,25,26] In four studies using Favipiravir it was found that there was no significant difference between the favipiravir group compared to the control group (8/112 (7.1%) vs. 7/119 (5.8%), p>0.05);[15] (19/75 (25.3) vs 10/74 (13.5), p=0.11);[16] (38 (64.4) vs 39 (65.0), p>0.05);[17](80 (74.1%) vs 33 (60.0%), p>0.05).[25] The most common adverse events reported were dizziness and nausea.[16] Meanwhile, the three studies using molnupiravir also consistently reported no significant difference in the occurrence of minor adverse events (216 (30.4%) vs. 231 (33.0%), p>0.05).[18] The most common minor adverse events related to molnupiravir therapy include nausea, diarrhea, and dizziness.[18,19] Gottlieb et al., 2022 reported several minor adverse events occurring in 118/279 participants (42.3%) in the remdesivir group and 131/283 participants (46.3%) in the placebo. The most common minor adverse events were nausea, headache, and cough but the difference were not statistically significant (p>0.05).[20] The incidence of minor adverse events in the nirmatrelvir plus ritonavir group compared with placebo was not significant (= 251 (22.6%) vs 266 (23.9%), p>0.05), in detail the minor adverse events that occurred included dysgeusia, diarrhea, fibrin D-dimer increase, mild transaminitis, and headache.[21] In a study conducted by Ramachandran et al., 2022, it was found that umifenovir showed few minor adverse events such as nasal discharge, headache, and stomach ache which were distributed almost similar to the placebo group (p>0.05).[23]

Serious Adverse Events

Eight studies are reporting serious adverse events after receiving antiviral therapy.[16,18–22,25,27] Two favipiravir-related studies showed consistently insignificant results between the favipiravir group compared to controls in which the study conducted by Holubar et al., 2021 reported serious adverse events in the placebo group. In contrast, serious adverse events did not occur in the favipiravir group (p> 0.05).[16] In addition, a study conducted by Ruzhentsova et al., 2021 reported that 2 participants (1.9%) experienced serious adverse events, while in the controls group there were no serious adverse events (p>0.05).[25] Serious adverse events include bone fracture and a decrease in saturation[25]. Meanwhile, serious adverse events were also found in molnupiravir, Bernal et al., 2022 reported that there were at least 49 (6.9%) participants experiencing serious adverse events when compared to the control group with 67 (9.6%) participants experiencing serious adverse events, this number is less numerically, but in an insignificant manner (p>0.05).[18] In addition, Fischer et al., 2022 reported four serious adverse events requiring hospitalization. Two participants in the 400 mg molnupiravir experienced a cerebrovascular accident and the other experienced a decrease in oxygen saturation, while those in 800 mg molnupiravir experienced acute respiratory failure. Therefore, despite the treatment with molnupiravir, the worsening condition of COVID-19 was suspected to be the cause, considering that in the placebo group one participant experienced acute respiratory failure cause hypoxia that led to death 31 days after the onset of serious adverse events.[19]

Administration of remdesivir in COVID-19 outpatients reported some serious adverse events than placebo 5 of 279 participants (1.8%) vs. 19 of 283 participants (6.7%).[20] More serious adverse events were reported in the lopinavir-ritonavir group compared with placebo (20/232 (8.6%) vs 12/220 (5.5%).) In the tenofovir disoproxil fumarate plus emtricitabine, two (6%) participants experienced serious adverse events, while one (3%) participant experienced serious adverse events in the standard therapy group.[27] In detail, two serious adverse events in the tenofovir disoproxil fumarate plus emtricitabine experienced dyspnea (22 breaths/min), very high RT-PCT viral load (14 Ct), and inflammatory syndrome (CRP = 21 mg/L) and one other participant need hospitalization for severe

COVID-related pneumonia requiring high flow oxygen, which recovered without mechanical ventilation. One participant in the standard of care group experienced severe COVID-related pneumonia requiring oxygen (6 L/min) and recovered.[27]

DISCUSSION

Prevention of COVID-19 illness progression is an important topic to minimize mortality risk, and antivirals have the potential because apart from the therapeutic effect they are not affected by the SARS-CoV-2 spike protein mutation.[28] In this study, several antivirals as monotherapy or combination have gone through clinical trials in early disease COVID-19 outpatients, including favipiravir, molnupiravir, remdesivir, umifenovir, tenofovir disoproxil fumarate, nirmatrelvir plus ritonavir, lopinavir plus ritonavir, and sofosbuvir plus daclatasvir.

The use of favipiravir showed conflicting results in time to alleviation of symptoms in which two studies had insignificant results,[15,16] while one study was significant.[25] This could be influenced by the different baseline characteristics among the three RCTs, where insignificant results were found in patients with mild disease, while an acceleration of time to alleviate symptoms occurred in patients with moderate disease. In addition, different initiations of favipiravir may influence the outcome which in Bosaeed et al., 2022 was initiated in the first 5 days of the onset.[15] Meanwhile, Ruzhentsova et al., 2021 initiated favipiravir administration within 3-6 days.[25] In addition, the consistent administration of favipiravir increased the rate of viral clearance significantly compared to the standard therapy group on the third and fifth days. However, above the 7th day, there was no difference. This maybe correlated with negative RT-PCR results where the number of negative RT-PCRs on day 5 is significant compared to controls,[25] while on day 7 the results are insignificant.[16] However, favipiravir consistently does not reduce the risk of hospitalization in COVID-19 outpatients.[15,16,25] Meanwhile, an RCT conducted by Ruzhentsova et al., 2021 reported two serious adverse events on favipiravir administration, including bone fractures and decreased saturations, but these were not correlated with investigational drugs. The most common non-serious adverse events were dizziness and nausea.[25] Nevertheless, favipiravir has been used in various countries such as China, Hungary, India, Korea, Poland, Portugal, Russia, Serbia, Thailand, and Turkey.[29] In the previous study, favipiravir did not reduce mortality and mechanical ventilation in moderate-severe patients.[30] Meanwhile, when used in mild to moderate, favipiravir could promote viral clearance, which is in line with the results of this study.[31]

In contrast to favipiravir, administration of molnupiravir in COVID-19 outpatients has been shown to reduce the risk of being hospitalized or dead compared to placebo. The mortality risk was lower by 89% with molnupiravir therapy.[18] In addition, molnupiravir was associated with greater reductions from baseline in mean viral load than placebo on days 3 and 5,[18,19] which is accompanied by a decrease in COVID-19 patients.[19] The serious adverse event of molnupiravir was not significant compared to placebo.[18,19] Molnupiravir was well tolerated with no increase in treatment-related or serious adverse events. In addition, there is no evidence of hematological, renal, or hepatic toxicity related to molnupiravir.[19] These results are in line with the previous systematic review which stated that molnupiravir could reduce disease progression and reduce the risk of hospitalization and/or death.[8] At the same time, in the safety profile, we found that there were serious adverse events that occurred although they were not statistically significant. Currently, there is no evidence that reports a mechanical relationship related to the duration of use and dosage of molnupiravir on serious adverse events such as acute respiratory failure. This opens the topic of the importance of a longer-term investigation of the safety profile of molnupiravir after receiving prophylaxis, which is currently still in the process of recruiting participants (ClinicalTrials.gov identifier: NCT04939428).

Like molnupiravir, remdesivir, and tenofovir disoproxil fumarate target the RNA-dependent RNA-Polymerase (RdRp) enzyme used by the coronavirus for transcription and replication of its viral RNA genome.[32] Administration of remdesivir

in COVID-19 outpatients showed a lower risk of hospitalization than in the placebo group. However, there was no difference in least-squares mean viral load change from baseline between remdesivir and placebo. In terms of safety profile, remdesivir caused nausea, headache, and cough the most but was insignificant when compared to placebo and the remdesivir group had few serious adverse events compared to placebo.[20] Administration of 3 days of remdesivir has qualitatively similar efficacy compared to single-dose neutralizing monoclonal antibodies.[33–35] However, intravenous administration of remdesivir is the same as neutralizing antibodies, which is less efficient than other oral antivirals. In this study, tenofovir disoproxil fumarate plus emtricitabine did not significantly improve COVID-19 symptoms compared to standard therapy.[27] In a study conducted by Parienti et al., 2021, gastrointestinal symptoms caused by COVID-19 may resemble tenofovir disoproxil fumarate plus emtricitabine adverse events, so the assessment of clinical tolerance and clinical resolution of symptoms may be biased.

Several antiviral protease inhibitors were analyzed in this study, including nirmatrelvir, lopinavir, and ritonavir.[21,22] The combined use of lopinavir-ritonavir did not reduce the risk of hospitalization compared to placebo in COVID-19 outpatients.[22] In contrast, the nirmatrelvir-ritonavir combination showed a lower hospitalization rate than the placebo in COVID-19 outpatients.[21] In addition, the risk of mortality was also decreased with nirmatrelvir-ritonavir compared with placebo, whereas with lopinavir-ritonavir there was no difference in mortality risk.[21,22] Next, for the virological outcomes was not associated with viral clearance. The safety profile of nirmatrelvir-ritonavir showed fewer serious adverse events than the placebo group.[21] In this study, the combination of nirmatrelvir plus ritonavir had better efficacy and safety than lopinavir plus ritonavir. Important, nirmatrelvir-ritonavir uses the unvaccinated and high-risk population, which is the most important population to receive interventions to prevent the progression of COVID-19. Unlike protease inhibitors and RNA synthesis inhibitors, umifenovir-related RCTs and the combination of sofosbuvir plus daclatasvir are still very limited. However, prior RCTs using umifenovir in COVID-19 outpatients have shown improvement in WHO clinical score analysis and greater viral clearance at day 5 if given earlier in mild disease.[23] Meanwhile, the combination of sofosbuvir plus daclatasvir did not show any reduction in COVID-19 symptoms when compared to standard therapy.[24] However, due to the lack of studies related to umifenovir and the combination of sofosbuvir plus daclatasvir, other RCTs are needed to confirm these results.

Real-world populations tend to have confounders that are difficult to control. For instance, patients may receive different standard therapies which may influence the outcomes. Additionally, population of these studies are COVID-19 outpatient in which the severity criteria of the disease varies between each centers.[36] This could lead to differences in clinical outcome. Thus, the administration of standard therapy such us corticosteroids and hydroxychloroquine on top of the antiviral therapy could potentially obscure the effects of antivirals in COVID-19 outpatients, especially in viral clearance and COVID-19 related hospitalization endpoint. It is also important to note that the small sample size could affect the findings of this study.

To the best of our knowledge, this is the first systematic review investigating the efficacy and safety of various antivirals in COVID-19 outpatient. However, this systematic review has some limitations. First, this study mainly discusses Favipiravir and molnupiravir because most published RCTs are both favipiravir and molnupiravir associated studies, and existing studies on antivirals are scarce. Second, several RCTs have small samples which can undermine the result and cause failure in detecting slight differences. Third, some studies did not have comparable RCTs so results still need to be confirmed. Therefore, further studies are required to address the limitation of our systematic review.

CONCLUSION

Various antivirals show different therapeutic effects in COVID-19 outpatients. Favipiravir

has shown inconsistent results concerning the time of improvement in COVID-19 symptoms and is more optimal when used in early disease. Meanwhile, molnupiravir has shown consistent results, which can reduce the risk of hospitalization and mortality, this is supported by a decreased change of viral load compared to baseline. Remdesivir and the combination of antivirals nirmatrelvir-ritonavir may have potential because they can prevent the progression of COVID-19 in early disease. However, the conclusion remains inconclusive due to limited data and the number of studies related to remdesivir and nirmatrelvir-ritonavir combinations. The safety profile of antivirals is relatively safe where there are no greater serious adverse events than controls. Therefore, further studies are needed to confirm this finding.

AUTHORS' CONTRIBUTIONS STATEMENT

DSB developed conceptualization, data curation, methodology, visualization, writing - original draft, writing - review & editing. PO developed conceptualization, data curation, writing - original draft, writing - review & editing. TPA developed writing - review & editing, manuscript validation, and supervision, PL developed conceptualization, writing - review & editing, data analysis, manuscript validation, and supervision. FA and RI contributed to the writing review and editing, and visualization. TT, DF and NL developed data curation and methodology. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

We declare no competing interests.

ACKNOWLEDGMENTS

The authors acknowledge the support and facilities received from Faculty of Medicine, Universitas Airlangga.

REFERENCES

1. Li Q, Guan X, Wu P, et al. Early transmission dynamics in wuhan, china, of novel coronavirus–infected pneumonia. N Engl J Med. 2020;382:1199–207. https://doi.org/10.1056/NEJMoa2001316.
2. WHO. Coronavirus disease (COVID-19) situation reports. Coronavirus Disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update 2022. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (accessed May 15, 2022).
3. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020:m1091. https://doi.org/10.1136/bmj.m1091.
4. García LF. Immune response, inflammation, and the clinical spectrum of COVID-19. Front Immunol. 2020;11:1441. https://doi.org/10.3389/fimmu.2020.01441.
5. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody ly-cov555 in outpatients with COVID-19. N Engl J Med. 2021;384:229–37. https://doi.org/10.1056/NEJMoa2029849.
6. Choi HM, Moon SY, Yang HI, Kim KS. Understanding viral infection mechanisms and patient symptoms for the development of COVID-19 therapeutics. IJMS. 2021;22:1737. https://doi.org/10.3390/ijms22041737.
7. Chugh H, Awasthi A, Agarwal Y, Gaur RK, Dhawan G, Chandra R. A comprehensive review on potential therapeutics interventions for COVID-19. European Journal of Pharmacology 2021;890:173741. https://doi.org/10.1016/j.ejphar.2020.173741.
8. Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: A systematic review of literature. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2021;15:102329. https://doi.org/10.1016/j.dsx.2021.102329.
9. Hung Y-P, Lee J-C, Chiu C-W, et al. Oral nirmatrelvir/ritonavir therapy for COVID-19: the dawn in the dark? Antibiotics. 2022;11:220. https://doi.org/10.3390/antibiotics11020220.
10. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol. 2020;92:418–23. https://doi.org/10.1002/jmv.25681.
11. Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. Proc Natl Acad Sci USA. 2017;114:206–14. https://doi.org/10.1073/pnas.1617020114.
12. Hessel MHM, Cohen AF, Rissmann R. Sofosbuvir and daclatasvir. Br J Clin Pharmacol. 2016;82:878–9. https://doi.org/10.1111/bcp.13011.
13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021:n71. https://doi.org/10.1136/bmj.n71.
14. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019:l4898. https://doi.org/10.1136/bmj.l4898.
15. Bosaeed M, Alharbi A, Mahmoud E, et al. Efficacy of favipiravir in adults with mild COVID-19: a randomized, double-blind, multicentre, placebo-controlled clinical trial. Clinical Microbiology and

Infection. 2022;28:602–8. https://doi.org/10.1016/j.cmi.2021.12.026.
16. Holubar M, Subramanian A, Purington N, et al. Favipiravir for treatment of outpatients with asymptomatic or uncomplicated COVID-19: a double-blind randomized, placebo-controlled, phase 2 trial. Infectious Diseases. (except HIV/AIDS); 2021. https://doi.org/10.1101/2021.11.22.21266690.
17. Lowe DM, Brown L-AK, Chowdhury K, et al. Favipiravir, lopinavir-ritonavir or combination therapy (Flare): a randomised, double blind, 2x2 factorial placebo-controlled trial of early antiviral therapy in COVID-19. Infectious Diseases (except HIV/AIDS). 2022. https://doi.org/10.1101/2022.02.11.22270775.
18. 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;386:509–20. https://doi.org/10.1056/NEJMoa2116044.
19. Fischer WA, Eron JJ, Holman W, et al. A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med. 2022;14:eabl7430. https://doi.org/10.1126/scitranslmed.abl7430.
20. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. N Engl J Med. 2022;386:305–15. https://doi.org/10.1056/NEJMoa2116846.
21. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med. 2022;386:1397–408. https://doi.org/10.1056/NEJMoa2118542.
22. Reis G, Moreira Silva EA dos S, Medeiros Silva DC, et al. Effect of early treatment with hydroxychloroquine or lopinavir and ritonavir on risk of hospitalization among patients with COVID-19: the together randomized clinical trial. JAMA Netw Open. 2021;4:e216468. https://doi.org/10.1001/jamanetworkopen.2021.6468.
23. Ramachandran R, Bhosale V, Reddy H, et al. Phase iii, randomized, double-blind, placebo controlled trial of efficacy, safety and tolerability of antiviral drug umifenovir vs standard care of therapy in non-severe COVID-19 patients. International Journal of Infectious Diseases. 2022;115:62–9. https://doi.org/10.1016/j.ijid.2021.11.025.
24. Roozbeh F, Saeedi M, Alizadeh-Navaei R, et al. Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. Journal of Antimicrobial Chemotherapy. 2021;76:753–7. https://doi.org/10.1093/jac/dkaa501.
25. Ruzhentsova TA, Oseshnyuk RA, Soluyanova TN, et al. Phase 3 trial of coronavir (Favipiravir) in patients with mild to moderate COVID-19. Am J Transl Res. 2021;13:12575–87.
26. Khoo SH, Fitzgerald R, Fletcher T, et al. Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a Phase I, open-label, dose-escalating, randomized controlled study. Journal of Antimicrobial Chemotherapy. 2021;76:3286–95. https://doi.org/10.1093/jac/dkab318.
27. Parienti J-J, Prazuck T, Peyro-Saint-Paul L, et al. Effect of Tenofovir Disoproxil Fumarate and Emtricitabine on nasopharyngeal SARS-CoV-2 viral load burden amongst outpatients with COVID-19: A pilot, randomized, open-label phase 2 trial. EClinicalMedicine. 2021;38:100993. https://doi.org/10.1016/j.eclinm.2021.100993.
28. McCullough PA, Kelly RJ, Ruocco G, et al. Pathophysiological basis and rationale for early outpatient treatment of sars-cov-2 (COVID-19) infection. The American Journal of Medicine. 2021;134:16–22. https://doi.org/10.1016/j.amjmed.2020.07.003.
29. Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. International Journal of Infectious Diseases. 2021;102:501–8. https://doi.org/10.1016/j.ijid.2020.10.069.
30. Özlüşen B, Kozan Ş, Akcan RE, et al. Effectiveness of favipiravir in COVID-19: a live systematic review. Eur J Clin Microbiol Infect Dis. 2021;40:2575–83. https://doi.org/10.1007/s10096-021-04307-1.
31. Manabe T, Kambayashi D, Akatsu H, Kudo K. Favipiravir for the treatment of patients with COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 2021;21:489. https://doi.org/10.1186/s12879-021-06164-x.
32. Cannalire R, Cerchia C, Beccari AR, Di Leva FS, Summa V. Targeting sars-cov-2 proteases and polymerase for COVID-19 treatment: state of the art and future opportunities. J Med Chem. 2022;65:2716–46. https://doi.org/10.1021/acs.jmedchem.0c01140.
33. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate COVID-19. N Engl J Med. 2021;385:1382–92. https://doi.org/10.1056/NEJMoa2102685.
34. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2021;325:632. https://doi.org/10.1001/jama.2021.0202.
35. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with sars-cov-2 neutralizing antibody sotrovimab. N Engl J Med. 2021;385:1941–50. https://doi.org/10.1056/NEJMoa2107934.
36. Budi DS, Rofananda IF, Pratama NR, et al. Ozone as an adjuvant therapy for COVID-19: A systematic review and meta-analysis. International Immunopharmacology. 2022;110:109014. https://doi.org/10.1016/j.intimp.2022.109014.