Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Microbiology, Immunology and Infection 54 (2021) 767—775

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Review Article

Clinical efficacy of antiviral agents against coronavirus disease 2019: A systematic review of randomized controlled trials

Chih-Cheng Lai [a], Chien-Ming Chao [b], Po-Ren Hsueh [c,d,*]

[a] *Department of Internal Medicine, Kaohsiung Veterans General Hospital, Tainan Branch, Tainan, Taiwan*
[b] *Department of Intensive Care Medicine, Chi Mei Medical Center, Liouying, Tainan, Taiwan*
[c] *Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[d] *Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*

Received 12 April 2021; accepted 18 May 2021
Available online 26 June 2021

KEYWORDS
COVID-19;
SARS-CoV-2;
Antiviral agents;
Efficacy

Abstract Despite aggressive efforts on containment measures for the coronavirus disease 2019 (COVID-19) pandemic around the world, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is continuously spreading. Therefore, there is an urgent need for an effective antiviral agent. To date, considerable research has been conducted to develop different approaches to COVID-19 therapy. In addition to early observational studies, which could be limited by study design, small sample size, non-randomized design, or different timings of treatment, an increasing number of randomized controlled trials (RCTs) investigating the clinical efficacy and safety of antiviral agents are being carried out. This study reviews the updated findings of RCTs regarding the clinical efficacy of eight antiviral agents against COVID-19, including remdesivir, lopinavir/ritonavir, favipiravir, sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, baloxavir, umifenovir, darunavir/cobicistat, and their combinations. Treatment with remdesivir could accelerate clinical improvement; however, it lacked additional survival benefits. Moreover, 5-day regimen of remdesivir might show adequate effectiveness in patients with mild to moderate COVID-19. Favipiravir was only marginally effective regarding clinical improvement and virological assessment based on the results of small RCTs. The present evidence suggests that sofosbuvir/daclatasvir may improve survival and clinical outcomes in patients with COVID-19. However, the sample sizes for analysis were relatively small, and all studies were exclusively conducted in Iran. Further larger RCTs in other countries are warranted to support these findings. In contrast, the present findings of limited RCTs did not

* Corresponding author. Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, Number 7, Chung-Shan South Road, Taipei, 100, Taiwan.
E-mail address: hsporen@ntu.edu.tw (P.-R. Hsueh).

https://doi.org/10.1016/j.jmii.2021.05.011

indicate the use of lopinavir/ritonavir, sofosbuvir/ledipasvir, baloxavir, umifenovir, and darunavir/cobicistat in the treatment of patients hospitalized for COVID-19.

Introduction

Since the end of 2019, when coronavirus disease 2019 (COVID-19) was first identified, more than 123 million people have been infected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1–3] Moreover, more than 2.7 million deaths have been caused by the COVID-19 pandemic.[3] Despite aggressive efforts on containment measures for the COVID-19 pandemic around the world, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is continuously spreading.[4–9] Therefore, there is an urgent need for effective antiviral agents.[10] To date, many studies have been performed to develop different approaches to COVID-19 therapy. In addition to early observational studies, which could be limited by study design, small sample size, non-randomized design, or different treatment timings, an increasing number of randomized controlled trials (RCTs) investigating the clinical efficacy of antiviral agents, including remdesivir, lopinavir/ritonavir, favipiravir, sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, baloxavir, umifenovir, darunavir/cobicistat, and their combinations, are being carried out. Most of these drugs repurpose per se and do not explore off-target secondary pharmacology. Among them, remdesivir, favipiravir, sofosbuvir/daclatasvir, and sofosbuvir/ledipasvir act as nucleoside analogs. Lopinavir/ritonavir and darunavir/cobicistat belonged to protease inhibitors. Baloxavir is new endonuclease inhibitor and umifenovir is a hemagglutinin inhibitor. In this study, we systematically searched the literature for phase III RCTs on antiviral agents for the treatment of COVID-19 and aimed to provide an update on the most effective antiviral agents among those currently available.

Remdesivir

Remdesivir is an RNA polymerase inhibitor that shows activity against RNA viruses belonging to Coronaviridae and Flaviviridae.[11] Therefore, it has been proposed as a potential anti-SARS-CoV-2 agent. Six RCTs[12–17] have been conducted to assess its efficacy and safety in the treatment of patients with COVID-19. First, Wang et al. conducted a randomized, double-blind, placebo-controlled, multicenter trial in Hubei, China, in which 237 adults with severe COVID-19 were enrolled and randomly assigned to remdesivir (n = 158) and control (n = 79) groups. In this study, remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio, 1.23; 95% confidence interval [CI], 0·87–1·75).[17] Second, a multicenter and multinational RCT included a total of 1062 adult patients hospitalized due to evident lower respiratory tract infection. The patients were randomly assigned to remdesivir (541 patients under treatment for 10 days) and placebo (521 patients) groups for evaluation.[12] The remdesivir group had a shorter median recovery time (10 days vs. 15 days; ratio for recovery rate, 1.29; 95% CI, 1.12–1.49; $p < 0.001$, using a log-rank test) than the placebo group; nevertheless, no significant difference was observed between the remdesivir and placebo groups with respect to mortality on day 15 (6.7% vs. 11.9%) and day 29 (11.4% vs. 15.2%) (hazard ratio, 0.73; 95% CI, 0.52–1.03).[12] Third, Goldman et al. compared the clinical efficacy of 5- and 10-day remdesivir regimens in the treatment of hospitalized patients with severe COVID-19.[13] A total of 397 patients underwent randomization and received remdesivir treatment (200 patients for 5 days and 197 for 10 days) in this study. No significant difference was observed between a 5-day and a 10-day course of remdesivir concerning clinical improvement of two points or more on the ordinal scale (64% vs. 54%, $p = 0.14$). Fourth, Spinner et al. conducted a randomized, open-label trial of hospitalized patients with moderate COVID-19 pneumonia to compare the efficacy of 5 or 10 days of remdesivir treatment with that of standard care, as determined by clinical status distribution on day 11 after initiation of treatment.[16] In this study, a total of 596 patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), and standard care (n = 200), respectively. On day 11, the 5-day remdesivir group had statistically significantly higher odds of a better clinical status distribution than the group receiving standard care (odds ratio, 1.65; 95% CI, 1.09–2.48), but the clinical status distribution on day 11 between the 10-day remdesivir and standard care groups was not significantly different ($p = 0.18$). Moreover, all-cause mortality on day 28 was 1% for the 5-day remdesivir group (log-rank test, $p = 0.43$ vs. standard care), 2% for the 10-day remdesivir group ($p = 0.72$ vs. standard care), and 2% for the standard care group.[16] Fifth, according to the interim report of the World Health Organization Solidarity trial, in which 11,330 adults underwent randomization and 2750 were assigned to receive remdesivir, no significant difference was observed between remdesivir and control groups regarding risk of in-hospital mortality (mortality rate ratio, 0.95; 95% CI, 0.81–1.11).[15] Finally, Kalil et al. further investigated the effect of remdesivir plus baricitinib on hospitalized adults with COVID-19 in a randomized, double-blind, placebo-controlled trial including a total of 1033 patients; 515 patients were assigned to combination treatment and 518 to control.[14] The combination group had a shorter recovery time (rate ratio, 1.16; 95% CI, 1.11–1.32) and higher odds of clinical improvement (odds ratio, 1.3; 95% CI, 1.0–1.6) than the control group. In contrast, no significant difference was observed between the combination and control groups with respect to 28-day mortality (5.1% vs. 7.8%,

hazard ratio, 0.65; 95% CI, 0.39—1.09).[14] In summary, treatment with remdesivir accelerated clinical improvement but lacked additional survival benefit. However, further subgroup analysis is warranted to identify the specific group that has benefited from remdesivir treatment.

Lopinavir/ritonavir

Lopinavir acts as an inhibitor of human immunodeficiency virus type 1 aspartate protease and exhibits *in vitro* inhibitory activity against SARS-CoV.[18,19] Moreover, ritonavir can extend the plasma half-life of lopinavir by inhibiting cytochrome P450. Several RCTs have been conducted to investigate the efficacy and safety of oral lopinavir/ritonavir against SARS-CoV-2 infection.[15,20—22] The first single-center RCT was conducted in Hubei, China, which included a total of 199 adult patients with severe COVID-19 randomly assigned in a 1:1 ratio to receive either lopinavir/ritonavir (400 mg/100 mg, orally) twice daily for 14 days along with standard care or standard care alone.[20] No difference was observed between the treatment group and standard care group with respect to the time to clinical improvement (hazard ratio, 1.31; 95% CI, 0.95—1.80) and mortality on day 28 (19.2% vs. 25.0%; 95% CI, −17.3—5.7).[20] Another single-center study in China enrolled patients with mild/moderate COVID who were randomly assigned to receive lopinavir/ritonavir (n = 34) and a control group that was not administered any antiviral medication (n = 17); no significant difference was observed between the intervention and control groups in terms of virological eradication rate on day 7 (35.3% vs. 41.2%) and day 14 (85.3% vs. 76.5%).[21] A multicenter trial was conducted in UK, in which 1616 patients were randomly allocated to receive lopinavir/ritonavir and 3424 patients to receive standard care, and showed similar findings in both the groups; lopinavir/ritonavir group was not associated with significant reduction in 28-day mortality (23% vs. 22%, $p = 0.60$), duration of hospital stay (median 11 days [interquartile range (IQR) 5 to >28] in both groups), or risk of progress to invasive mechanical ventilation or death (risk ratio 1·09, 95% CI 0·99—1·20) compared with the standard care group.[22]To summarize all these findings and the interim report of the World Health Organization Solidarity trial,[15] the use of lopinavir/ritonavir for the treatment of hospitalized patients COVID-19 is not supported.

Favipiravir

Favipiravir is an RNA-dependent RNA polymerase inhibitor that behaves as a purine analog that inhibits viral DNA replication.[23] It is a prodrug that can be ribosylated and phosphorylated to convert it into its active metabolite, favipiravir ibofuranosyl-5′-triphosphate. The report of the interim results of a phase II/III multicenter RCT conducted in Russia revealed that the viral clearance rate on day 5 in patients treated with favipiravir was significantly higher than that under standard care (62.5% [25/40] vs. 30.0% [6/20], $p = 0.018$), however, the difference was not statistically significant on day 10 (92.5% [37/40] vs. 80.0% [16/20], $p = 0.155$).[24] In addition, favipiravir was associated with a shorter time to defervescence than the control (2 days [IQR 1—3] vs. 4 days [IQR 1—8], $p = 0.007$).[24]

Udwadia et al. conducted a phase 3, open-label, multicenter trial, which included 150 patients with confirmed mild/moderate COVID-19, who were randomized to favipiravir (n = 75) and control (n = 75) groups.[25] They observed shorter median time to the cessation of viral shedding in the favipiravir group than that in the control group (5 days vs. 7 days, $p = 0.129$), but the difference was not statistically significant. However, they found that the median time to the cessation of clinical cure was significantly shorter for the favipiravir group than for the control group (3 days vs. 5 days, $p = 0.030$).[25]

Khamis et al. compared the effectiveness of favipiravir combined with inhaled interferon beta-1b and hydroxychloroquine in an open-label RCT, which included 89 adult patients hospitalized with moderate to severe COVID-19 pneumonia.[26] However, there were no significant differences in the levels of inflammatory biomarkers at hospital discharge between the study and control groups indicated by $p > 0.05$ for C-reactive protein, ferritin, lactate dehydrogenase, and interleukin-6; moreover, there were no significant differences between the two groups with regard to the overall length of hospital stay (7 days vs. 7 days; $p = 0.948$), transfer to the intensive care unit (ICU) (18.2% vs. 17.8%; $p = 0.960$), discharge rate (65.9% vs. 68.9%; $p = 0.764$), and overall mortality (11.4% vs. 13.3%; $p = 0.778$).[26]

An exploratory RCT conducted in China included 30 hospitalized patients with COVID-19 who were randomly assigned in a 1:1:1 ratio to baloxavir marboxil, favipiravir, and control groups, respectively.[27] This study showed no significant difference in the percentage of patients who turned virus-negative after a 14-day treatment (77% vs. 100%) and the time to clinical improvement (14 days vs. 15 days) between the favipiravir and control groups.[27]

Dabbous et al. compared the efficacy of favipiravir with that of chloroquine against COVID-19 in a multicenter RCT including 96 patients and found that none of the patients in the favipiravir group needed mechanical ventilation in contrast to the chloroquine group (n = 3). Moreover, the favipiravir group had a shorter mean duration of hospitalization than the chloroquine group (13.3 ± 5.9 days vs. 15.9 ± 4.8 days, $p = 0.06$). In addition, two patients (mortality rate, 4.2%) in the chloroquine group and one (2.3%) in the favipiravir group was deceased ($p = 1.00$).[28]

The effect of early vs. late treatment initiation of favipiravir was assessed in a prospective, randomized, open-label trial for adolescent and adult patients hospitalized for asymptomatic/mild COVID-19.[29] There was no significant difference in viral clearance after 6 days of treatment between the two groups (66.7% vs. 56.1%; adjusted hazard ratio [aHR], 1.42; 95% CI, 0.76—2.62). In contrast, early treatment was associated with shorter time to defervescence than late treatment (2.1 days vs. 3.2 days; aHR, 1.88; 95% CI, 0.81—4.35).[29]

Sofosbuvir/daclatasvir and sofosbuvir/ledipasvir

Sofosbuvir has a broad antiviral spectrum against many species of the Flaviviridae and Togaviridae families, including the yellow fever,[30] Zika,[31] dengue,[32] and

chikungunya viruses,[33] and its combination with daclatasvir has been used against hepatitis C in Iran.[34] Four RCTs[35–38] were conducted in Iran to evaluate the clinical efficacy and safety of sofosbuvir/daclatasvir (400/60 mg) for the treatment of patients with COVID-19. First, a single-center trial was conducted to assess the efficacy of sofosbuvir/daclatasvir plus ribavirin for treating hospitalized patients with moderate COVID-19.[35] Although the sofosbuvir/daclatasvir plus ribavirin group had a significantly shorter recovery time (6 [5–7] days vs. 6 [5–8] days, $p = 0.033$) than control group, no significant difference was observed between the sofosbuvir/daclatasvir plus ribavirin group (n = 24) and the standard care group (n = 24) regarding duration of hospital stay (6 days vs. 6 days, $p = 0.398$), mortality rate (0% vs. 3%, $p = 0.234$), and ICU admission (0% vs. 17%, $p = 0.109$). Moreover, there were two major limitations of this study, including a very small sample size and an imbalance in the baseline characteristics between the arms.[35] Second, Sadeghi et al. conducted an open-label, multicenter trial to evaluate the effect of sofosbuvir/daclatasvir on the clinical outcomes in patients with moderate or severe COVID-19.[37] In this trial, 66 patients were randomly allocated to either treatment arm (n = 33) or control arm (n = 33); sofosbuvir/daclatasvir treatment significantly shortened the duration of hospital stay compared with standard care alone (6 days vs. 8 days, $p = 0.029$). Additionally, the probability of hospital discharge was significantly higher for the treatment arm than for the control arm (Gray's test $p = 0.041$). However, no significant difference was observed in terms of clinical recovery rate after 14 days (88% vs. 67%, $p = 0.076$) and mortality rate (9% [n = 3] vs. 15% [n = 5], $p = 0.708$).[37] Third, another RCT compared the effectiveness of sofosbuvir/daclatasvir and ribavirin in treating patients with severe COVID-19, and observed that the sofosbuvir/daclatasvir group (n = 35) was associated with a shorter duration of hospital stay (5 days vs. 9 days, $p < 0.01$), a lower risk of ICU admission (17% vs. 48%, $p = 0.01$), and mortality (5.7% vs. 33%, $p = 0.01$) than the ribavirin group (n = 27).[36] Fourth, the effect of sofosbuvir/daclatasvir on COVID-19 outpatients was evaluated in a double-blind RCT including 55 patients, and no significant difference was observed in symptoms, including fever, cough, sore throat, headache, myalgia, xerostomia, and olfactory loss on day 7 between the treatment (n = 27) and control (n = 28) groups.[38] Moreover, fewer hospitalizations (however, not statistically significant) were observed in the sofosbuvir/daclatasvir group than in the control group (1 vs. 4). A meta-analysis included these four RCTs[35–38] and observed that sofosbuvir/daclatasvir-based treatment was associated with higher clinical recovery (rate ratio [RR], 1.20; 95% CI, 1.04–1.38), lower mortality rate (RR, 0.31; 95% CI, 0.12–0.78), and fewer ICU admissions (RR, 0.33; 95% CI, 0.15–0.72) than standard care or other alternative treatment in the management of patients with COVID-19.[39] These findings suggest the potential of sofosbuvir/daclatasvir-based treatment for patients with COVID-19. However, all these studies[35–38] were conducted in Iran; the results might not be generalizable, and therefore, a large multinational study is warranted to uphold this conclusion.

Another RCT was conducted in Iran for assessing the efficacy and safety of another combination, sofosbuvir/ledipasvir, against mild to moderate COVID-19.[40] In this open-label clinical trial, 82 patients were randomly assigned to receive either sofosbuvir/ledipasvir (400/100 mg daily) along with standard care (n = 42) or standard care alone (n = 40) for 10 days. Although the clinical response rates, duration of hospital and ICU stay, and 14-day mortality were comparable between the groups, the clinical recovery time was significantly shorter in the sofosbuvir/ledipasvir group than in the control group (2 days vs. 4 days, $p = 0.02$).[40] Nonetheless, the sample size was small, and therefore, RCTs with large sample sizes are necessary to further investigate the efficacy of sofosbuvir/ledipasvir.

Umifenovir

Umifenovir is a hemagglutinin inhibitor that can effectively block the fusion of influenza virus with its host cell and is effective against all strains of influenza viruses (A, B, and C), especially influenza A viruses (H1N1, H2N2, and H3N3), and has few side effects.[41] Recently, two RCTs[21,42] were conducted to assess its efficacy for the treatment of COVID-19. In the ELACOI trial,[21] patients with mild/moderate COVID were randomly assigned to receive umifenovir (n = 35) and no antiviral medication (control group, n = 17); no significant difference was observed between the intervention and control groups regarding virological eradication rate on day 7 (37.1% vs. 41.2%) and day 14 (91.4% vs. 76.5%), the duration from positive-to-negative conversion of SARS-CoV-2 nucleic acid (9.1 days vs. 9.3 days), and the rate of clinical deterioration from moderate to severe/critical status (8.6% vs. 11.8%) (all $p > 0.05$). In addition, no significant difference was observed in other secondary outcomes, including the rate of antipyresis, cough resolution, and improvement of chest computed tomography score on day 7 and day 14 (all $p > 0.05$). Another study recruited 100 hospitalized patients with COVID-19 who were randomly assigned to two groups of hydroxychloroquine followed by lopinavir/ritonavir and hydroxychloroquine followed by umifenovir.[42] They found that the umifenovir group was associated with a shorter duration of hospital stay (7.2 days vs. 9.6 days, $p = 0.02$) and higher peripheral oxygen saturation level on day 7 (94% vs. 92%, $p = 0.02$) than the lopinavir/ritonavir group. In contrast, no significant difference was observed with respect to the time to defervescence (2.7 days vs. 3.1 days, $p = 0.2$) and the risk of intubation (6% vs. 4%, $p = 0.6$) and mortality (2% vs. 4%, $p = 0.5$).[42] However, both these studies have small sample sizes to draw any conclusion, and further study on the effectiveness of umifenovir against COVID-19 using a larger sample size and multicenter design is warranted.

Baloxavir

Baloxavir marboxil is a prodrug that is metabolized to its active form, baloxavir acid, and the first cap-dependent endonuclease enzyme inhibitor that can block influenza virus replication.[43] Most clinical studies have focused on its

Table 1 The characteristics of randomized controlled studies.

Author, year of report	Study site	Study duration	Size of study group (intervention)	Size of control group (comparator)	Primary outcome	Main findings
Remdesivir						
Beigel et al., 2020[12]	Multicenter in 10 countries	Between February 21 and April 19, 2020	541	521 (Placebo)	Time to recovery	10 (9–11) vs. 15 (13–18) day; recovery rate ratio, 1.29; 95% CI, 1.12–1.49
Goldman et al., 2020[13]	55 hospitals in eight countries	Between March 6 and March 26, 2020	200 (5-days)	197 (10-days)	A clinical improvement of two points or more on the ordinal scale on day 14	64% vs. 54% ($p = 0.14$)
Kalil et al., 2021[14]	67 sites in eight countries:	Between May 8 and July 1, 2020	515 (plus baricitinib)	518 (placebo)	Time to recovery	7 days vs. 8 days; recovery rate ratio, 1.16; 95% CI, 1.01–1.32
Pan et al., 2021[15]	405 hospitals in 30 countries	From March 22 to October 4, 2020	2750	2725 (no trial drug)	In-hospital mortality	Rate ratio, 0.95; 95% CI, 0.81–1.11
Spinner et al., 2020[16]	105 hospitals in the US, Europe, and Asia	Between March 15 and April 18, 2020	197 (10-days), 199 (5-days)	200 (standard care)	Clinical status on day 11 on a 7-point ordinal scale	65% (10-days) vs. 70% (5-days) vs. 61% (standard care); 5-days vs. control; 9.7 (0.1–19.1); 10-days vs. control, 4.8 (−2.0–14.4)
Wang et al., 2020[17]	10 hospitals in Hubei, China	Between Feb 6 and March 12, 2020	158	78 (Placebo)	Time to clinical improvement within 28 days	21 (13–28) vs. 23 (15–28) day; hazard ratio, 1.23; 95% CI, 0.87–1.75
Lopinavir/ritonavir						
Pan et al., 2021[15]	405 hospitals in 30 countries	From March 22 to October 4, 2020	1411	1380 (no trial drug)	In-hospital mortality	Rate ratio, 1.00; 95% CI, 0.79–1.25
Cao et al., 2020[20]	Single-center in Hubei Province, China	From January 18 to February 3, 2020	99	100 (standard care)	Time to clinical improvement	Hazard ratio, 1.31; 95% CI, 0.95–1.80
Li et al., 2020[21]	Single center in China	From February 1 to March 28, 2020	34	17 (no antiviral medication)	Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid	Virological eradication rate on day 7 (35.3% vs. 41.2%) and 14 (85.3% vs. 76.5%); both $p > 0.05$
RECOVERY Collaborative Group, 2020[22]	176 hospitals in the UK	Between March 19 and June 29, 2020	1616	3424 (usual care)	28-day all-cause mortality	23% vs. 22%, rate ratio 1·03, 95% CI, 0·91–1·17
Favipiravir						
Ivashchenko et al., 2020[24]	6 sites in Russia	Between April and May 2020	40	20 (standard care)	Elimination of SARS-CoV-2 on day 10	92.5% vs. 80.0%, $p = 0.155$
Udwadia, 2021[25]	7 sites in India	From May 14 to July 3, 2020	75	75 (standard care)	Time to the cessation of viral shedding	5 days vs. 7 days, $p = 0.129$

(*continued on next page*)

Table 1 (*continued*)

Author, year of report	Study site	Study duration	Size of study group (intervention)	Size of control group (comparator)	Primary outcome	Main findings
Khamis et al., 2020[26]	Single center in Oman	From June 22 to August 13, 2020	44 (plus inhaled interferon beta-1b)	45 (HCQ)	Improvement in levels of inflammatory markers	No significant difference for CRP, ferritin, LDH, and IL-6 (all $p > 0.05$)
Lou et al., 2021[27]	Single center in China	Since February 3, 2020	9	10	Percentage of subjects with viral negative test on day 14 and the time from randomization to clinical improvement	77% vs. 100%, $p > 0.05$ 14 (6—38) days vs. 15 (6—24) days, $p > 0.05$
Dabbous et al., 2021[28]	Multicenter in Egypt	From April to August 2020	44	48 (CQ)	Duration of hospitalization	13.3 ± 5.9 days vs. 15.9 ± 4.8 days, $p = 0.06$
Doi et al., 2020[29]	25 hospitals in Japan	From March 2 to May 18, 2020	44 (early treatment)	45 (late treatment)	Viral clearance on day 6	66.7% vs. 56.1%, hazard ratio, 1.42; 95% CI, 0.76—2.62
Sofosbuvir/daclatasvir						
Abbaspour Kasgari et al., 2020[35]	Single center in Iran	Between March 20 and April 8, 2020	24 (plus ribavirin)	24	Duration of hospital stay	6 [5—7] days vs. 6 [5—8] days, $p = 0.033$
Eslami et al., 2020[36]	Single center in Iran	Between March 18 and April 16, 2020	35	27 (ribavirin)	Duration of hospital stays	5 days vs. 9 days, $p < 0.01$
Sadeghi et al., 2020[37]	Multicenter in Iran	Between March 26 and April 26, 2020	33	33	Clinical recovery within 14 days	88% vs. 67%, $p = 0.076$
Roozbeh et al., 2021[38]	Single center in Iran	Between April 8 and May 19, 2020	27 (plus HCQ)	28 (HCQ)	Symptom alleviation after 7 days of follow-up	No significant difference in symptom response for fever, cough, sore throat, headache, myalgia, xerostomia, and olfactory loss (all $p > 0.05$)
Sofosbuvir/ledipasvir						
Khalili et al., 2020[40]	Single center in Iran	NA	42	40 (standard care)	Clinical response	90.48% vs. 92.5%, $p = 0.65$
Umifenovir						
Li et al., 2020[21]	Single center in China	From February 1 to March 28, 2020	35	17 (no antiviral medication)	Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid	Virological eradication rate on day 7 (37.1% vs. 41.2%) and 14 (91.4% vs. 76.5%) both $p > 0.05$
Nojomi et al., 2020[42]	Single center in Iran	Between April 20 and June 18, 2020	50	50 (HCQ)	Hospitalization duration and clinical improvement after 7 days of admission	7.2 days vs. 9.6 days, $p = 0.02$ 94% vs. 92%, $p = 0.02$

Baloxavir						
Lou et al., 2021[27]	Single center in China	Since February 3, 2020	10	10	Percentage of subjects with viral negative test on day and the time from randomization to clinical improvement	70% vs. 100%, $p > 0.05$ 14 (6–49) days vs. 15 (6–24) days, $p > 0.05$
Darunavir/cobicistat						
Chen et al., 2020[48]	Single center in China	From January 30 to February 6, 2020	15	15	Virological clearance rate of oropharyngeal swabs on day 7	46.7% vs. 60.0%, $p = 0.72$

CRP, C-reactive protein; LDH, lactate dehydrogenase; IL-6, interleukin-6; HCQ, hydroxychloroquine; CQ, chloroquine; NA, not applicable.

efficacy in influenza,[44–47] and only one RCT was conducted to assess its effect on SARS-CoV-2 infection.[27] The study demonstrated that baloxavir was not associated with higher rates of virological eradication and clinical improvement than standard care (virological eradication after 14-day treatment: 70% vs. 100%; the time to clinical improvement: 14 days vs. 15 days).[27] A similar trend was found in the secondary outcomes, including rates of incidence of mechanical ventilation (10% vs. 0%) and ICU admission (10% vs. 0%). The lack of efficacy of baloxavir in this study might be attributable to delay in randomization and treatment with baloxavir after onset of symptoms (12.7 ± 3.5 days). In addition, the study number was limited (baloxavir group, n = 10; control group, n = 10); therefore, larger studies are warranted in future.

Darunavir/cobicistat

Darunavir is a human immunodeficiency virus-1 protease inhibitor that has a mechanism of action similar to that of lopinavir. A single-center RCT was conducted in China to investigate the efficacy and safety of darunavir/cobicistat in treating pneumonia caused by SARS-CoV-2.[48] A total of 30 participants were enrolled in this study, and all received interferon alpha-2b and standard care. Each study group, the treatment group (1 pill of darunavir/cobicistat (800 mg/150 mg) per day for 5 days), and the control group (no oral antiviral drug), included 15 participants. No significant difference was observed between the study and control groups regarding the proportion of positive-to-negative conversion of SARS-CoV-2 on day 7 (intention-to-treat population, 46.7% vs. 60.0%, $p = 0.72$; per-protocol population, 50.0% vs. 60.0%, $p = 0.72$) and viral clearance rate (hazard ratio, 0.82; 95% CI, 0.36–1.88). One patient in the study group progressed to acute respiratory distress syndrome requiring mechanical ventilation, but all patients in the control group remained stable on day 14 ($p = 1.0$).[48] Therefore, the study findings and study design (small size and open-label) did not support the use of darunavir/cobicistat for the treatment of patients with COVID-19.

Conclusion

This review discussed the results of several RCTs regarding the clinical efficacy of eight antiviral agents against COVID-19, including remdesivir, lopinavir/ritonavir, favipiravir, sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, baloxavir, umifenovir, darunavir/cobicistat, and their combinations (Table 1). Treatment with remdesivir could accelerate clinical improvement, however, lacked additional survival benefits. Moreover, 5-day regimen of remdesivir might show adequate effectiveness for the treatment of patients with mild to moderate COVID-19. Favipiravir was only marginally effective regarding clinical improvement and virological assessment based on the results of small-size RCTs. The present evidence suggests that sofosbuvir/daclatasvir may improve survival and clinical recovery in patients with COVID-19. However, the sample sizes for analysis were relatively small, and all studies were exclusively conducted in Iran. Further larger

RCTs in other countries are warranted to support these findings. In contrast, the present findings of limited RCTs, it did not suggest the use of lopinavir/ritonavir, sofosbuvir/ledipasvir, baloxavir, umifenovir, and darunavir/cobicistat in the treatment of patients hospitalized for COVID-19. In addition to the above anti-viral agents, molnupiravir - the prodrug of the active antiviral ribonucleoside analog ß-d-N4-hydroxycytidine can efficiently inhibit SARS-CoV-2 replication in human lung tissue[49] and is currently in phase II/III clinical trials after successfully passing phase I trial.[50] Although many anti-viral agents showed promising *in vitro* activity against SARS-CoV-2, most of them exhibited limited clinical efficacy. At this moment, we should keep work hard to develop the effective antiviral agents during this pandemic.

Funding

None.

Ethical approval

Not required.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

References

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents* 2020;**55**:105924.
2. Lai CC, Wang CY, Wang YH, Hsueh SC, Ko WC, Hsueh PR. Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. *Int J Antimicrob Agents* 2020;**55**:105946.
3. WHO. https://covid19.who.int/, 2021. [Accessed 23 March 2021].
4. Hsih WH, Cheng MY, Ho MW, Chou CH, Lin PC, Chi CY, et al. Featuring COVID-19 cases via screening symptomatic patients with epidemiologic link during flu season in a medical center of central Taiwan. *J Microbiol Immunol Infect* 2020;**53**:459—66.
5. Huang WH, Teng LC, Yeh TK, Chen YJ, Lo WJ, Wu MJ, et al. 2019 novel coronavirus disease (COVID-19) in Taiwan: reports of two cases from Wuhan, China. *J Microbiol Immunol Infect* 2020;**53**:481—4.
6. Huang YC, Lee PI, Hsueh PR. Evolving reporting criteria of COVID-19 in Taiwan during the epidemic. *J Microbiol Immunol Infect* 2020;**53**:413—8.
7. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths. *J Microbiol Immunol Infect* 2020;**53**:404—12.
8. Lee CY, Wang PS, Huang YD, Lin YC, Hsu YN, Chen SC. Evacuation of quarantine-qualified nationals from Wuhan for COVID-19 outbreak - Taiwan experience. *J Microbiol Immunol Infect* 2020;**53**:392—3.
9. Yen MY, Schwartz J, Chen SY, King CC, Yang GY, Hsueh PR. Interrupting COVID-19 transmission by implementing enhanced traffic control bundling: implications for global prevention and control efforts. *J Microbiol Immunol Infect* 2020;**53**:377—80.
10. Chen PL, Lee NY, Cia CT, Ko WC, Hsueh PR. A review of treatment of coronavirus disease 2019 (COVID-19): therapeutic repurposing and unmet clinical needs. *Front Pharmacol* 2020;**11**:584956.
11. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine c-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. *J Med Chem* 2017;**60**:1648—61.
12. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med* 2020;**383**:1813—26.
13. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in patients with severe Covid-19. *N Engl J Med* 2020;**383**:1827—37.
14. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2021;**384**:795—807.
15. Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed antiviral drugs for Covid-19 - interim WHO Solidarity trial results. *N Engl J Med* 2021;**384**:497—511.
16. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *J Am Med Assoc* 2020;**324**:1048—57.
17. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020;**395**:1569—78.
18. Chen F, Chan KH, Jiang Y, Kao RY, Lu HT, Fan KW, et al. *In vitro* susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol* 2004;**31**:69—75.
19. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004;**59**:252—6.
20. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;**382**:1787—99.
21. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. *Med (N Y)* 2020;**1**:105—113.e4.
22. Group RC. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2020;**396**:1345—52.
23. Sood S, Bhatia GK, Seth P, Kumar P, Kaur J, Gupta V, et al. Efficacy and safety of new and emerging drugs for COVID-19: favipiravir and dexamethasone. *Curr Pharmacol Rep* 2021 Feb 18:1—6. https://doi.org/10.1007/s40495-021-00253-w.
24. Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, et al. Avifavir for treatment of patients with moderate COVID-19: interim results of a phase II/III multicenter randomized clinical trial. *Clin Infect Dis* 2020 Aug 9:ciaa1176. https://doi.org/10.1093/cid/ciaa1176.
25. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial. *Int J Infect Dis* 2021;**103**:62—71.
26. Khamis F, Al Naabi H, Al Lawati A, Ambusaidi Z, Al Sharji M, Al Barwani U, et al. Randomized controlled open label trial on the

use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia. *Int J Infect Dis* 2021;**102**:538—43.
27. Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, et al. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. *Eur J Pharmaceut Sci* 2021;**157**:105631.
28. Dabbous HM, Abd-Elsalam S, El-Sayed MH, Sherief AF, Ebeid FFS, El Ghafar MSA, et al. Efficacy of favipiravir in COVID-19 treatment: a multi-center randomized study. *Arch Virol* 2021;**166**:949—54.
29. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. *Antimicrob Agents Chemother* 2020;**64**. e01897-20.
30. de Freitas CS, Higa LM, Sacramento CQ, Ferreira AC, Reis PA, Delvecchio R, et al. Yellow fever virus is susceptible to sofosbuvir both in vitro and in vivo. *PLoS Neglected Trop Dis* 2019;**13**:e0007072.
31. Bullard-Feibelman KM, Govero J, Zhu Z, Salazar V, Veselinovic M, Diamond MS, et al. The FDA-approved drug sofosbuvir inhibits Zika virus infection. *Antivir Res* 2017;**137**:134—40.
32. Gan CS, Lim SK, Chee CF, Yusof R, Heh CH. Sofosbuvir as treatment against dengue? *Chem Biol Drug Des* 2018;**91**:448—55.
33. Ferreira AC, Reis PA, de Freitas CS, Sacramento CQ, Villas Bôas Hoelz L, Bastos MM, et al. Beyond members of the Flaviviridae family, sofosbuvir also inhibits Chikungunya virus replication. *Antimicrob Agents Chemother* 2019;**63**. e01389-18.
34. Merat S. SD1000: high sustained viral response rate in 1361 patients with hepatitis C genotypes 1, 2, 3, and 4 using a low-cost, fixed-dose combination tablet of generic sofosbuvir and daclatasvir: a Multicenter, phase III clinical Trial. *Clin Infect Dis* 2020;**70**:2206—12.
35. Abbaspour Kasgari H, Moradi S, Shabani AM, Babamahmoodi F, Davoudi Badabi AR, Davoudi L, et al. Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial. *J Antimicrob Chemother* 2020;**75**:3373—8.
36. Eslami G, Mousaviasl S, Radmanesh E, Jelvay S, Bitaraf S, Simmons B, et al. The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19. *J Antimicrob Chemother* 2020;**75**:3366—72.
37. Sadeghi A, Ali Asgari A, Norouzi A, Kheiri Z, Anushirvani A, Montazeri M, et al. Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): a randomized controlled trial. *J Antimicrob Chemother* 2020;**75**:3379—85.
38. Roozbeh F, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, Merat S, Wentzel H, et al. Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. *J Antimicrob Chemother* 2021;**76**:753—7.
39. Chan HT, Chao CM, Lai CC. Sofosbuvir/daclatasvir in the treatment of COVID-19 infection: a meta-analysis. *J Infect* 2020 Dec 26;**S0163—4453**(20):30783—90. https://doi.org/10.1016/j.jinf.2020.12.021.
40. Khalili H, Nourian A, Ahmadinejad Z, Emadi Kouchak H, Jafari S, Dehghan Manshadi SA, et al. Efficacy and safety of sofosbuvir/ledipasvir in treatment of patients with COVID-19; A randomized clinical trial. *Acta Biomed* 2020;**91**:e2020102.
41. Leneva IA, Falynskova IN, Makhmudova NR, Poromov AA, Yatsyshina SB, Maleev VV. Umifenovir susceptibility monitoring and characterization of influenza viruses isolated during ARBITR clinical study. *J Med Virol* 2019;**91**:588—97.
42. Nojomi M, Yassin Z, Keyvani H, Makiani MJ, Roham M, Laali A, et al. Effect of arbidol (umifenovir) on COVID-19: a randomized controlled trial. *BMC Infect Dis* 2020;**20**:954.
43. Shirley M. Baloxavir marboxil: a review in acute uncomplicated influenza. *Drugs* 2020;**80**:1109—18.
44. Hayden FG, Sugaya N, Hirotsu N, Lee N, de Jong MD, Hurt AC, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *N Engl J Med* 2018;**379**:913—23.
45. Baker J, Block SL, Matharu B, Burleigh Macutkiewicz L, Wildum S, Dimonaco S, et al. Baloxavir marboxil single-dose treatment in influenza-infected children: a randomized, double-blind, active controlled phase 3 safety and efficacy trial (miniSTONE-2). *Pediatr Infect Dis J* 2020;**39**:700—5.
46. Ikematsu H, Hayden FG, Kawaguchi K, Kinoshita M, de Jong MD, Lee N, et al. Baloxavir marboxil for prophylaxis against influenza in household contacts. *N Engl J Med* 2020;**383**:309—20.
47. Ison MG, Portsmouth S, Yoshida Y, Shishido T, Mitchener M, Tsuchiya K, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. *Lancet Infect Dis* 2020;**20**:1204—14.
48. Chen J, Xia L, Liu L, Xu Q, Ling Y, Huang D, et al. Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. *Open Forum Infect Dis* 2020;**7**:ofaa241.
49. Wahl A, Gralinski LE, Johnson CE, Yao W, Kovarova M, Dinnon 3rd KH, et al. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. *Nature* 2021;**591**:451—7.
50. Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut N, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. *Antimicrob Agents Chemother* 2021 Mar 1. https://doi.org/10.1128/AAC.02428-20. AAC.02428-20.