Available online **www.ijpras.com**

International Journal of Pharmaceutical Research & Allied Sciences, 2021, 10(3):94-111
https://doi.org/10.51847/E3AXGWu0IP

Review Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Evidence of the Clinical Efficacy of Antiviral Agents against SARS-CoV-2

Angelique Welman[1*], Kim Outhoff[1]

[1]Department of Pharmacology, University of Pretoria, Pretoria, South Africa.

***Email:** u18017046@tuks.co.za*

ABSTRACT

The highly transmissible SARS-CoV-2, the virus that causes COVID-19, typically induces atypical pneumonia in humans by replicating in the lower and upper respiratory tract. It may also infect gastrointestinal and cardiovascular tissue, where its key binding receptor, ACE2 is located. Numerous treatment strategies have been investigated and repurposed to mitigate the potentially serious clinical outcomes of the COVID-19 pandemic. Yet there is currently no definitive treatment for this disease. This literature review examined the published clinical evidence of potential anti-SARS-CoV-2 antiviral drug efficacy in terms of reducing viral load, recovery time, hospitalization time, mechanical ventilation, and case fatality rates in COVID-19 patients.
It was found that remdesivir, the FDA-approved antiviral for severe illness, shows suboptimal efficacy, that neutralizing antibodies including bamlanivimab/etesevimab, casirivimab/imdevimab, and CT-P59 demonstrate clinical efficacy, particularly in reducing SARS-CoV-2 viral loads and curbing hospitalization and death, and that antivirals such as favipiravir, sofosbuvir/daclatasvir, and nitazoxanide may harbor potential efficacy. Nafamostat-mesylate and novaferon require further investigation to validate promising early findings. In conclusion, definitive treatments of COVID-19 remain elusive, but numerous antiviral strategies including remdesivir and neutralizing antibodies may temper COVID-19. Prevention of COVID-19 may be achieved by vaccination, but only a small proportion of the global population is inoculated. Therefore, ongoing research on anti-SARS-CoV-2 treatment is required.

Key words: *COVID-19, SARS-CoV-2, Neutralizing antibodies, Remdesivir, Bamlanivimab/etesevimab*

INTRODUCTION

In Wuhan, China in December 2019 a virus related to the acute respiratory syndrome (ARDS) -like bat viruses emerged, known as the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) SARS-CoV-2 most likely emerged in bats, mutated in an intermediate species, and became transmissible to humans [1-3]. The virus is rapidly transmitted through droplets and aerosolized particles [1, 4] and has an estimated mean and median incubation period of 7.8 and 5.01 days, respectively (0-14 days) [5, 6]. Infected individuals may present with fever, dry cough, loss of taste and smell, and shortness of breath, although upper respiratory tract or gastrointestinal symptoms may also be present. Mild illness may progress to moderate and/or severe pneumonia and ARDS that requires oxygen, sometimes by mechanical ventilation, in a hospital setting. A hypercoagulable state is often present [7-9]. COVID-19 has a case fatality rate of approximately 2-3%. There is a 6-41-day window to show symptoms up until death when affected (14-day median) and this depends on age and immune status [7, 10].
Imaging studies in severe COVID-19, show alveolar damage in concordance with hyaline membrane formation, severe pneumonia, and ARDS [9, 10]. High levels of inflammation in the alveolar walls, shedding of pneumocytes, and intra-alveolar inflammatory infiltrates by neutrophils signifying secondary bacterial infection

are also evident [9, 10]. Furthermore, CT scans may show features such as acute cardiac injury, and grand-glass opacities that may result in death [7].

In common with SARS-CoV and MERS-CoV, SARS-CoV-2 is an RNA, unsegmented, positive sense, beta coronavirus with a transmembranous viral spike (S) fusion protein that is thought to bind to angiotensin-converting enzyme 2 (ACE2) receptors, present in epithelial cells of the lungs and gastrointestinal system, and to Angiotensin II receptor type 2 (AGTR2) to a lesser degree [11, 12].

The Spike protein consists of three receptor-binding domains (RBDs); the S1-subunit binds to the ACE2 receptor in an "up" conformation, after changing its conformation in a chain-like manner. The S2-subunit then binds in a more stable "down" conformation after the S1 is lost. S2 consists of heptad repeat 1 (HR1) and heptad repeat 2 (HR2) that interact to form a six-helical bundle (6-HB). After the 6-HB forms, the viral cell membrane fuses with the host cell membrane, resulting in infection [11, 12].

The transmissibility of SARS-CoV-2 is determined by the binding affinity between the ectodomain structure in the spike-protein and ACE2. SARS-CoV-2 has 10-20 times higher binding affinity than SARS-CoV to ACE2 receptors, which is why human to human transmission is higher in COVID-19 [11].

After host cellular entry occurs, SARS-CoV-2 RNA is released, followed by replication and transcription via protein cleavage and the replicase-transcriptase complex. After replication, translation, assembly, and packaging of viral structural proteins, viral particles are released in the host cell.

As ACE-2 receptors in alveolar epithelium are the main target and pathogenic mechanism of SARS-CoV-2 infection, it has been proposed that ACE2 inhibitors and ARBs act as potential SARS-CoV-2 antivirals. However, recent data suggest that these drugs result in poor outcomes when used as a treatment for COVID-19 [11, 13]. Supportive therapies include high flow oxygen or mechanical ventilation, which are critical to aid respiration in severe ARDS. Short-term glucocorticoid immunosuppressant therapy is used in severe inflammation and ARDS, which may be associated with hyperinflammation or cytokine storm. Glucocorticoids may also aid in complications like acute heart- and kidney injuries [11, 12].

The focus here, however, is on examining the evidence for repurposed antiviral agents that are effective against other RNA viruses, as well as for newly developed antivirals [11]. These include anti-SARS-CoV-2 neutralizing antibodies that can prevent viral attachment and entering host cells and commercially approved nucleoside analogs that may inhibit viral RNA synthesis by targeting RNA-dependant RNA polymerase [14]. Protease inhibitors and papain-like protease inhibitors that have demonstrated some efficacy in MERS and SARS may also prove useful in the treatment of COVID-19 [7, 14].

There have been no definitive effective therapeutic options for COVID-19. In addition, new SARS-CoV-2 variants have emerged, including the UK 501Y.V1 (alpha), the South African 501Y.V2 (beta), the Brasilian 501Y.V3(gamma), and the Indian B.1.671.2 (delta) [15, 16]. These variants have been found to have much higher transmission rates compared to previous variants possibly because of shorter incubation times and increased viral loads, which complicates the research and development of potential antiviral treatments [16]. This paper reviewed the evidence for antiviral agents potentially improving clinical outcomes including viral loads, symptoms, disease progression, recovery time, hospitalization, mechanical ventilation, hospital duration, and incidence of COVID-related death.

MATERIALS AND METHODS

Study design

All evidence on clinical trials investigating antivirals against SARS-CoV-2 was retrieved by searching the published literature with search engines including Prospero, Google Scholar, Ovid, and Cochrane databases using the following search terms:

"antivirals", safety and efficacy", "treatment/therapeutic options", "SARS-Co-V-2", "neutralizing antibodies", "nucleoside analogs", "protease inhibitors" in "COVID-19"

Additionally, COVID-NMA, which is a living systematic review and living mapping of COVID-19 trials, was searched. This tool identifies randomized controlled trials (RCTs) registered in the WHO International Clinical Trials Registry Platform, systematically searching the platform weekly for all RCTs that evaluate treatments and preventive interventions for COVID-19.

Sample size and collection

Articles were retrieved from several databases. Initially, titles and abstracts were screened, and duplicates were removed. All full-text English published articles of clinical and nonclinical trials of antiviral treatment against SARS-Co-V-2 or COVID-19 were screened.

Those that fulfilled the inclusion criteria were selected for data extraction. These were all published clinical trials, including randomized controlled trials and open-label clinical trials that focused on therapeutic options that specifically target SARS-CoV-2 in adults. Preclinical studies were included only if they assessed drugs that have not yet been evaluated in clinical trials.

Articles that addressed symptomatic COVID-19 treatment options were excluded. These were studies of glucocorticoids, colchicine, ivermectin, repurposed antimalarials such as chloroquine or hydroxychloroquine, and traditional Chinese medicine. Furthermore, all studies that included children and pregnant women were excluded, as well as preclinical studies of drugs that had clinical evidence.

A PRISMA diagram was used to outline the study flow.

Data were extracted from the eligible studies using amended Cochrane Library data extraction forms. Summarized outcomes included antiviral efficacy in terms of the type of study (RCT, placebo arm, open-label, non-clinical); mechanism of antiviral action; changes in viral loads; time to recovery; prevalence and duration of hospitalization; prevalence and duration of mechanical ventilation; and COVID-19 case fatality rate.

Where possible, these were expressed as number, mean, ranges, and percentages. These data were synthesized and discussed. Overall findings and conclusions were drawn.

RESULTS AND DISCUSSION

After applying the inclusion/exclusion criteria, 38 publications were assessed **(Figure 1, Table 1)**. These included 39 clinical trials involving 9 311 patients and 10 antiviral agents, which included remdesivir; favipiravir; ribavirin; sofosbuvir/daclatasvir; lopinavir/ritonavir; triazavirin; nitazoxanide; novaferon; darunavir/corbicistat; camostat-, gabexate-, and nafamostat-mesylate; as well as 3 neutralizing antibody cocktails including, bamlanivimab/etesivimab; casirivimab/imdevimab (REGN-COV-2); and CT-P53. These are discussed below.

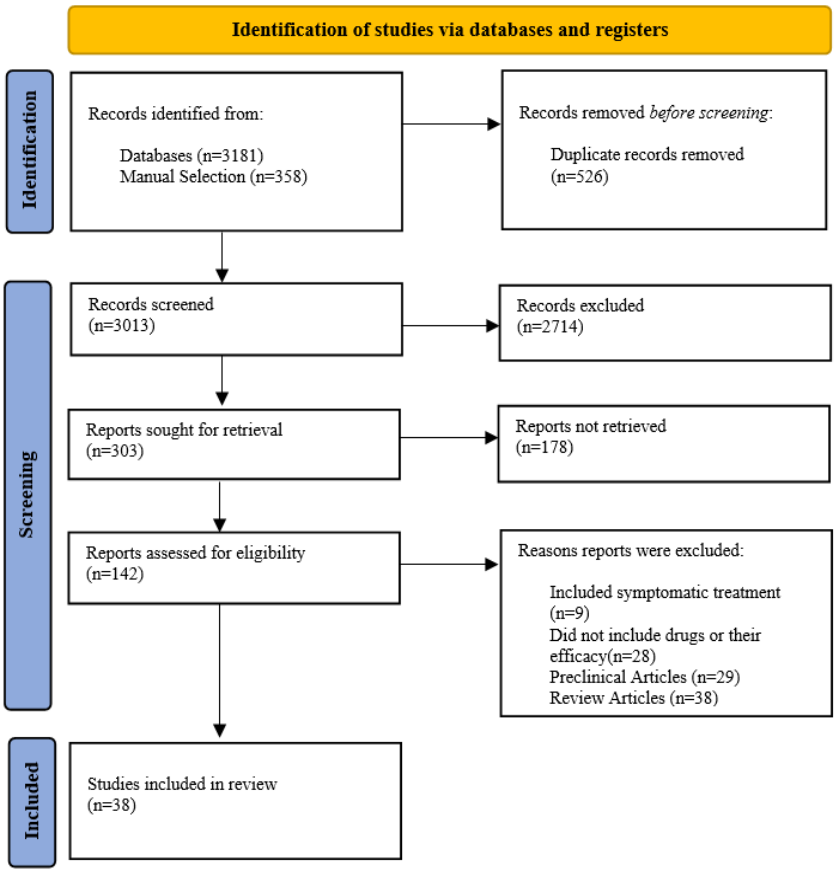

Figure 1. PRISMA diagram

Remdesivir (RDV)

Remdesivir (RDV), an antiviral, is a prodrug that passes through cell membrane easily where it is converted into its active triphosphate form (RDV-TP). In RNA viruses e.g. SARS-CoV-2, RDV-TP acts as a substrate for viral replicases and competes with endogenous adenosine-triphosphate to be incorporated into RNA strands, promoting the synthesis of delayed chain termination, and therefore inhibiting viral replication. It has been shown to inhibit the growth of severe acute pneumonia syndrome coronavirus 2 and the replication of Middle East Respiratory Syndrome Coronavirus [13, 17].

Eight RCTs, including the WHO's SOLIDARITY trial, involving a total of 4 829 patients, have tested the efficacy of RDV **(Table 1)**. Early studies, [17-20] showed promising results while later larger trials, [21-24] disputed these findings. Initial trials indicated that RDV showed potential, most notably in studies conducted by Wang *et al*. and Beigel *et al*. [17, 18]. A decrease in recovery time was observed in both studies, especially in patients on oxygen, although it only reached significance in the latter study of 541 patients. These findings resulted in RDV being approved for emergency treatment [13]. It should, however, be noted that both studies had several limitations due to COVID-19 restrictions, including their underpowered sample sizes, and the open-label design of one, which considering newer findings, may account for the misleading results of early studies [17, 18].

Two trials that were also of relatively small size (n =396) and (n=397), indicated possible efficacy of five-day RDV treatment that demonstrated significantly higher odds of clinical improvement compared to 10-day treatment. Yet overall, no statistical significance was seen between 5-day and 10-day therapy [19, 20].

The WHO's pivotal SOLIDARITY trial (n= 2 743) found that RDV treatment had no real effects on mortality or the course of the disease and did not show overall efficacy [24]. This study, supported by two other smaller studies, including a nor-solidarity trial, provided sufficient evidence to conclude that RDV has little efficacy to offer [22, 23]. Some improvement was seen when combining RDV with barcitinab, but this was not convincing [21].

Table 1. Remdesivir (RDV) treatment of COVID-19

Author/date	Study design/ number of participants (n)	Clinical outcome measures/primary endpoints	Main results
Wang Y *et al.* 2020 [17]	Double-blind, multicentre RCT, severe patients RDV (n=158) Placebo (n=79)	Time to clinical improvement (28d) Discharge from hospital	RDV vs placebo, no increased time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]) and (hazard ratio 1·52 [0·95–2·43) NS, treatment stopped early due to side effects, 12% vs 5%
Beigel *et al*. 2020 [18]	The adaptive COVID-19 treatment trial International double-blind RCT, hospitalized patients RDV (n=541) Placebo: (n= 521)	Recovery time	RDV vs placebo, significant reduction in time to recovery ($p < 0.001$]) notable in supplemental oxygen patients (RRR 1.47 [95% CI: 1.17–1.84]), non-significant reduction in mortality rates (14d), ($p = 0.06$])
Spinner *et al.* 2020 [19]	Phase 3 open-label, RCT, moderate patients 10-day RDV (n= 197) 5-day RDV (n= 199) Standard care (n =200)	Clinical status (11d) on 7-point ordinal scale	RDV vs placebo, significantly improved clinical status (11d) in 5-day group, (odds ratio 1.65 [95% CI: 1.09–2.48, $p = 0.02$]), no difference in 10-day group ($p = 0.18$ by Wilcoxon rank sum test)
Goldman *et al.* 2020 [20]	RCT, open-label, phase 3, hospitalized patients RDV 5-day (n= 200) RDV 10-day (n= 197)	Clinical status (14d) on 7-point ordinal scale	10-Day vs 5-day groups, clinical improvement of >2 points, 64% vs 54%, similar distribution in clinical status (14d), ($p= 0.14$), 10-day group had a significantly worse baseline clinical condition ($p=0.02$)
Barratt-Due *et al.* 2021	NOR-Solidarity, multi-country, open-label,	In-hospital mortality, admission	NS differences in primary endpoints

[23]	adaptive randomized trial, hospitalized patients. RDV (n=42) HCQ (n= 52) SoC (n = 87)	to ICU, and initiation of mechanical ventilation	
WHO Solidarity trial [24]	WHO SOLIDARITY trial RDV (n=2750) Control (n= 4088)	In-hospital deaths	RDV vs control, death in 301 of 2743 patients vs 303 of 2708 patients (rate ratio, 0.95; 95% CI, 0.81 to 1.11; p=0.50), no overall definitive efficacy in other endpoints
Kalil *et al.* 2021 [21]	Double-blind, RCT, hospitalized adults RDV + barcitinab (n= 515) RDV (n=518)	Recovery time SE: Clinical improvement (15d)	Combination vs RDV, Median recovery time 7d (95% CI, 6-8), vs 8d (rate ratio for recovery, 1.16; 95% CI, 1.01-1.32; (p= 0.03), higher improvement odds in clinical status (15d) (odds ratio, 1.3; 95% CI, 1.0-1.6), ventilated patients' recovery time, 11d vs 18d (rate ratio, 1.51; 95% CI, 1.10-2.08), mortality (28d), 5.1% vs 7.8% (hazard ratio for death, 0.65; 95% CI, 0.39-1.09), serious side effects and new infections, (16.0% vs. 21.0%; difference, −5.0 percentage points; 95% CI, −9.8 to −0.3; p= 0.03) and (5.9% vs. 11.2%; difference, −5.3 percentage points; 95% CI, -8.7 to -1.9; p= 0.003)
Mahajan *et al.* 2021 [22]	Prospective randomized trial, moderate/severe patients. RDV (n= 34) SoC (n=36)	Clinical status (14d), time to clinical improvement, recovery, and death	RDV vs SoC, no statistically significant difference in clinical status, time to recovery, oxygen therapy, or mortality (p= 0.749)

Legend: **RDV**: remdesivir; **RCT**: randomized, controlled trial; **NS**: not significant; **SoC**: standard of care

Favipiravir (FPV)

Favipiravir (T-705) is an oral pyrazine derivative and a viral RdRp inhibitor. In influenza, for example, the active triphosphate form competes for RNA incorporation with ATP and GTP and it, therefore, functions as a nucleotide analog that causes chain termination and triggering of lethal viral mutagenesis through random point mutations. It has broad antiviral activity. Favipiravir has shown low efficacy in inhibiting SARS-CoV-2 in cell-based assays [13]. However, open-label clinical trials have shown FVP to have significant efficacy in reducing viral clearance [25-29]. **Table 2** summarizes the 6 clinical trials assessing favipiravir treatment of COVID-19. The most notable findings were provided by Zhao *et al*. [27], which reported significant reductions in several viral parameters after FPV administration [27]. In common with findings by Cai *et al.* [25] and Udwadia *et al*., [28] evidence suggests that FPV has some efficacy in reducing viral load. It was also noted that FPV showed higher efficacy when compared to chloroquine (QC), although this was not significant [26]. When combined with arbidol, no differences in rate to clinical recovery was seen [29]. All of these studies, however had limitations, suggesting room for more vigorous clinical testing and well-designed trials.

Table 2. Favipiravir (FPV) treatment of COVID-19

Author/date	Study design/number of participants (n)	Clinical outcome measures/primary endpoints	Main results
Cai *et al.* 2020 [25]	Open-label, non-randomized trial FPV (n=35) LPV/r (n=45)	Time of viral clearance and chest CT improvement (14d)	FPV vs control, shorter median viral clearance time, 4d (IQR: 2.5-9) vs 11d (IQR: 8-13), (p <0.001), significant higher improvement in chest CT,

	(Both groups combined with IFN-alpha 1b treatment)		91.43% vs 62.22%, (p = 0.004)
Dabbous *et al.* 2021 [26]	Multicenter, interventional phase 2/3 RCT, mild to moderate patients. FPV (n= 48) CQ (n=48)	Mortality rate and mechanical ventilation	FPV vs CQ, one death (2.3%), vs two (4.2%) (p = 1.00), lower hospitalization (p=0.06), not significantly associated with mortality (p = 0.615), no patients on mechanical ventilation in FPV (p = 0.129)
Chen *et al.* 2020 [29]	Prospective, multicentre, open-label, RCT FPV (n=116) Arbido l(n=120)	Clinical recovery rate (7d) SE: Fever duration, time to relief of cough, and auxiliary oxygen therapy/non-invasive mechanical ventilation	FPV vs arbidol, clinical recovery rate 71.43% vs 55.86% (p = 0.0199), significantly lower time to cough relief and fever reduction (both p <0.001), similar auxiliary oxygen therapy and non-invasive mechanical ventilation (both p >0.05), well-tolerated.
Zhao *et al.* 2021 [27]	Multicenter, open-label, RCT, SARS-CoV-2 RNA re-positive patients FPV (n=36) Control (n=19)	Time to receive twice consecutive negative RT-PCR results (>24h apart) for SARS-CoV-2 in nasopharyngeal and sputum samples	FPV vs control, significant shorter duration of primary endpoint (median 17 vs. 26 d); hazard ratio 2.1 (95% CI [1.1-4.0], p =0.038), increased virus shedding proportion (80.6% [29/36] vs. 52.6% [10/19], (p=0.030, respectively), significant decrease in CRP (p =0.016), mild adverse events
Udwadia *et al.* 2021 [28]	Randomized, multicenter, parallel-arm, open-label, phase 3 trial, mild/ moderate patients FPV (n=75) Contro l(n=75)	Time to viral shedding cessation and time to clinical cure	FPV vs control, median cessation of viral shedding duration of 5d (95% CI: 4d, 7d) vs 7d (95% CI: 5d, 8d), (p =0.129), median time to clinical cure, 3d (95% CI: 3d, 4d) vs 5d (95% CI: 4d, 6d), (p = 0.030), side effects 36% vs 8%.
Khamis *et al.* 2021 [30]	RCT, open-label, moderate/severe hospitalized patients FPV + IFN-beta (n=44) HCQ (n=45)	Hospitalization, discharge and lowered mortality (14d)	FPV and IFN-beta vs HCQ, no significant differences between hospitalization length, (7 vs 7d; p = 0.948), ICU transfer, (18.2% vs 17.8%; p = 0.960), hospital discharges, (65.9% vs 68.9%; p = 0.764), overall mortality, (11.4% vs 13.3%; p = 0.778)

Legend: **FPV**: favipiravir; **LPV/r**: lopinavir/ritonavir; **IFN**: inter-feuron; **IQR**: interquartile range; **CQ**: chloroquine; **HCQ**: hydroxychloroquine; **PCR**: polymerase chain reaction

Sofosbuvir/daclatasvir (SOF/DCV)

Sofosbuvir is a nucleotide analog that supresses positive sense RNA synthesis and is indicated for hepatitis C viral infection. It is combined with daclatasvir to provide broad antiviral activity by binding to RdRp and Main protease to inhibit their function [31].

This combination therapy showed no statistically significant improvement in remission or mortality when compared to lopinavir/ritonavir (LPV/r) [32] **(Table 3)**. SOF/DCV, however, significantly improved recovery rates [31, 33], as well as significantly reduced hospitalization [34, 35] compared to standard of care (SoC) control groups in two small studies. Evidence, therefore, is accumulating on the combination's efficacy in improving these outcomes and further studies may provide greater clarity on its role in treating COVID-19 [36].

Table 3. Sofosbuvir/daclatasvir (SOF/DCV) treatment of COVID-19

Author/date	Study design/ number of participants (n)	Clinical outcome measures/primary endpoints	Main results
Eslami *et al.* 2020 [31]	Open-label parallel trial RBV (n=27) SOF/DCV (n=35)	Hospital discharge time SE: ICU duration, side effects, laboratory values, respiratory rate, and mortality	RBV vs SOF/DCV, median hospitalization duration 9d vs 5d (p<0.01), 33% mortality vs 6% (p=0.01), relative death risk, 5.8% vs 0.17% (p= 0.02), median recovery time, 11d vs 6d (p<0.01)
Yakoot *et al.* 2020 [33]	RCT, parallel 2-arm, open-label SOF/DCV (n= 44) SoC (n= 45)	Proportion of clinical recovery (14d and 21d), respiratory rate, oxygen saturation, time to clinical recovery, time to viral negativity, mean clinical status change on an 8-point ordinal scale SE: Mechanical ventilation, Adverse events	SOF/DCV vs SoC, increased proportion of cumulative clinical recovery at 21d, 91% (91%; CI: 78.8-96.4%) versus 76% (77.8%;63.7-87.5%)), almost 1.6 times higher clinical recovery probability, statistically significant, greater efficacy in 8-point ordinal scale score, mean severity of lung lesions score, and case fatality rate; all not statistically significant, well-tolerated
Sadeghi *et al.* 2020 [35]	Open-label, multicentre, RCT, moderate/severe adults. (nSOF/DCV=33) (nSoC=33)	PE: Clinical recovery (within 14d) (normal fever and oxygen saturation) SE: All-cause mortality, mechanical ventilation, hospitalization duration, time to discharge.	SOF/DCV vs SoC, clinical recovery, 88% vs 67% (p= 0.076), shorter hospitalization duration [6days (IQR 4-8) vs (8 days (IQR 5-13)]; p= 0.029, Cumulative hospital discharge significantly higher, (Gray's P= 0.041). No serious adverse events
Yadollahzadeh *et al.* 2021 [32]	Randomized clinical trial. SOF/DCV (n= 58) LPV/r (n= 54)	Clinical recovery rate (oxygen saturation, normal respiration, and body temperature). SE: Relative radiological evidence for improvement, lesion progression, mechanical ventilation.	SOF/DCV Treatment: No significant differences in comorbidities, death, ICU, and remission. Lower hospital discharge rate compared to LPV/r, (HR=1.551 (95% CI=1.008-2.386), P-value=0.046). Better outcome by Hazard plot compared to LPV/r.
Roozbeh *et al.* 2021 [36]	Double-blind, RCT, in mild outpatients. SOF/DCV(n=27) HCQ(n=28)	Symptom alleviation after 7-day follow-up. SE: loss of appetite, dyspnoea, fatigue, and hospital admission, after 1-month follow-up.	SOF/DCV Treatment: Baseline characteristics similar in both groups, no significant differences in symptoms, 7d. Difference in hospitalization was not significant. Fatigue reduced after 1-month follow-up, 16 patients vs 2, P< 0.001.
Alavi-moghaddam *et al.* 2021 [34]	RCT, open-label, phase 2 in hospitalized patients. SOF(n=27) SoC(n=30)	Clinical recovery (normal body temperature and oxygen saturation). SE: All-cause mortality during hospitalization, or within 14 days to discharge.	SOF Treatment: Primary outcome achieved, 88.9% vs 33.3% in control(p<0.001) Significantly shorter median hospitalization time vs control [10days (IQR 5-12) vs 11.5 days (IQR 8.5-17.75)] (P = 0.016). All-cause mortality 2% vs 13%, not significant.

Legend: **PE**: primary endpoint

Lopinavir/ritonavir (LPV/r)

These antiretroviral (ARVs) protease inhibitors, used in a combination for HIV-1 treatment, primarily cause cleavage of HIV polyproteins. Ritonavir, a CYP 450 enzyme inhibitor, increases the bioavailability of lopinavir [13]. LPV/r has shown activity against SARS-CoV-2: Choy *et al.*, demonstrated mixed results *in vitro*, but reduced viral loads were observed [37]. Evidence suggests that treatment with LPV/r does not produce any real benefits in treating COVID-19 [38-40] **(Table 4)**. This combination did not reduce hospitalization time, symptoms, or mortality rates significantly when compared to arbidol or

hydroxychloroquine (HCQ) and showed a lack of benefits in time to clinical improvement, mortality, or hospitalization [38-40]. Most notably, the WHO SOLIDARITY trial (n=1 411) showed no significant clinical improvement with LPV/r usage [24].

Table 4. Lopinavir/ritonavir (LPV/r) in COVID-19

Author/date	Study design/ number of participants (n)	Clinical outcome measures/primary endpoints	Main results
Cao *et al.* 2020 [38]	RCT, open-label trial in hospitalized Adults. LPV/r (n= 99) SoC (n=100)	Time to clinical improvement (improvement of 2 points of 7-point ordinal scale or hospital discharge).	LPV/r vs SoC, No significant differences in time to clinical improvement (hazard ratio, 1.24; 95% [CI], 0.90-1.72), similar mortality, 28d (19.2% vs. 25.0%; difference, -5.8 percentage points; 95% CI, -17.3-5.7) time to clinical improvement shorter by 1 day (hazard ratio, 1.39; 95% CI, 1.00 to 1.91), detectable viral RNA similar at various time frames, GI adverse events more common
Li *et al.* 2020 [39]	Exploratory RCT, mild/moderate patients. LPV/r (n=34) Arbido l(n=35) Placebo (n=17)	Rate of positive-to-negative viral nucleic acid conversion. SE: clinical status (rate of antipyresis, rate of cough resolution, CT improvement rate (7d and 14d)	LPV/r vs arbidol vs placebo, primary endpoint similar between groups, (p >0.05), similar measurements of secondary endpoints (7d or 14d) (all p > 0.05), clinical status from moderate to severe in 23.5% of patients, vs 8.6% vs 11.8%
Reis *et al.* 2021 [40]	Randomized trial LPV/r (n= 244) HCQ (n=214) Placebo (n=227)	Hospitalization and death (90d) SE: All-cause hospitalization, side effects, symptom resolution, and viral clearance	LPV/r vs HCQ vs placebo, hospitalization, 5.7% vs 3.7% vs 4.8%, differences not statistically significant HCQ: hazard ratio [HR], 0.76 [95% CI, 0.30-1.88]; LPV/r: HR, 1.16 [95% CI, 0.53-2.56], Differences in viral clearance not statistically significant (14d) (hydroxychloroquine: [OR], 0.91[95% CI, 0.82-1.02]; lopinavir-ritonavir: OR, 1.04 [95% CI, 0.94-1.16])
WHO Solidarity trial [24]	WHO Solidarity trial LPV (n=1411) Control (n=4088)	Mortality, ventilation, or hospitalization duration	LPV vs control, Death in 148/1399 patients vs 146/1372, No significant reductions in any endpoints

Legend: **GI**: Gastrointestinal tract; **WHO**: World Health Organization

Table 5 summarises all clinical research articles of miscellaneous agents that include ribavirin, triazavirin, nitazoxanide, novaferon, darunavir/cobicistat, and camostat mesylate treatment.

Ribavirin (RBV)

Ribavirin, a guanosine analog, incorporates into RNA strands, and thereby obstructs RNA synthesis. It has mutagenic effects in viruses such as influenza and decreases GTP pools [13]. Its efficacy in COVID-19 appears to be limited, although it has shown antiviral effects against coronaviruses *in-vitro* [41]. In a study of 10 SARS isolates, *in vivo* ribavirin showed little to no efficacy and was not recommended as a candidate drug to evaluate clinically [42]. Ribavirin's efficacy in severe COVID-19 patients was, however, evaluated in three studies, but little efficacy was found in clinical improvement when using this drug as monotherapy [43], or in combination with lopinavir/ritonavir [44] or sofosbuvir/daclatasvir [45] **(Table 5)**.

Triazavirin (TZV)

TZV has been marketed in Russia since 2015. It inhibits the viral ribonucleic acid synthesis and viral replication of certain fragments of the genome [46]. TZV shows broad-spectrum antiviral properties, and computational *in silico* studies have shown that it binds to structural proteins in SARS-CoV-2, such as E- and

S-proteins as well as non-structural 3-chymotrypsin-like protease. It has also shown some binding affinity to ACE-2 in humans [47]. However, in a small double-blind RCT, no differences were observed in time to clinical improvement [46] **(Table 5)**. Another clinical trial on TZV (ChiCTR2000030001) is currently underway [48].

Nitazoxanide (NTZ)

Nitazoxanide was originally used as an anti-protozoal, but it has broad-spectrum antiviral properties. It interferes with viral replication pathways including interferon signaling and host-regulated pathways. The mechanism may vary from virus to virus. NTZ inhibited SARS-CoV-2 by 90% *in-vitro*, [49] and showed promising efficacy in several parameters, including significantly reducing SARS-CoV-2 viral loads, [49-52] and immune markers [49] **(Table 5)**. It has also shown efficacy in reducing hospitalization and disease progression, 48] and potential to treat COVID-19 symptoms [51]. Studies suggest that NTZ provides more clinical benefits, including reducing viral loads, time to recovery, and hospitalization, compared to placebo [52].

Novaferon

Fang *et al*. investigated the efficacy of novaferon, a broad-spectrum antiviral used for chronic hepatitis B infection. Novaferon is a more potent non-natural protein of subtypes of human interferon alpha-2b created by modified DNA shuffling technology [53]. This drug was tested *in vitro* where it inhibited viral replication as well as prevented viral infection in cells. In a small clinical study, novaferon alone, as well as in combination with LPV/r, significantly increased viral clearance rates, suggesting its potential efficacy [53] **(Table 5)**. Further investigation as a candidate anti-SARS-CoV-2 agent is recommended.

Darunavir/cobicistat (DRV)

Darunavir is an HIV-1 protease inhibitor, while corbistat increases its plasma half-life. They are therefore used in combination. Compared to remdesivir, DRV did not show any inhibition of SARS-CoV-2 *in vitro* [54]. Meanwhile, only two clinical studies have reported on the effects of DRV/c, and both indicated no significant evidence of improvement with DVR/c [55] **(Table 5)**. In fact, this combination may be dangerous when treating hospitalized COVID-19 patients, as an exploratory retrospective study emphasized its lack of efficacy and highlighted the higher ventilation and mortality rates compared to controls [56].

Camostat-, gabexate-, nafamostat-mesylate

Comastat, gabexate and nafamostat mesylate are synthetic protease inhibitors of epithelial TMPRSS2 and may act as host cell entry inhibitors by reducing priming of viral S-proteins [57, 58]. *In vitro* testing suggested that nafamostat mesylate has an almost 15-fold higher SARS-CoV-2 inhibition efficiency compared to camostat and gabexate [59]. One clinical study showed that camostat mesylate increased time to clinical improvement and reduced mortality, although these were not statistically significant **(Table 5)**. An increase in median change in viral load to day 5, was, however, significant [58]. Preclinical evidence, however, suggests that nafamostat may be a better option than camostat [59].

A single case study reports on three cases of elderly patients with severe COVID-19 pneumonia who showed improvement in clinical status after nafamostat treatment after 15 days of hospitalization [60]. Three clinical trials that are currently evaluating nafamostat's efficacy (NCT04418128, NCT04352400, NCT04473053), may support its use in COVID-19 [61].

Table 5. Miscellaneous potential treatments for COVID-19

Ribavirin (RBV)			
Author/date	**Study design/ number of participants (n)**	**Clinical outcome measures/primary endpoint**	**Main results**
Tong *et al.* 2020 [43]	Retrospective cohort study, severe patients. RBV (n=44) Control (n=71)	Negative conversion tome for SARS-CoV-2 RT-PCR SE: Mortality rate	RBV vs control, 12.8 ± 4.1 days vs 14.1 ± 3.5 days negative conversion time (P = 0.314), 17.1% deaths vs 24.6% (P = 0.475), similar adverse events.

Huang *et al.* 2020 [44]	Single-center, randomized, open-label, prospective trial. (n=101) ratio 1:1:1 (nRBV + IFN-a) (nLPV/r + IFN-a) (nRPV + nLPV/r + IFN-a)	Median difference in interval to viral nucleic acid negativity, proportion with nucleic acid negativity (14d), mortality (28d), proportion re-classified as severe, adverse events	RBV + IFN-alpha vs LPV vs combination, median interval from baseline nucleic acid negativity, 13d vs 12d vs 15d(p=0.23), proportion patients with nucleic acid negativity (14d), 51.5%, vs 61.1%, and 46.9%, p<0.05, illness progression, 3.0% vs 5.6% and 6.3%, not significant, adverse events significantly higher in combination group.
Kasgari *et al.* 2020 [45]	Single-centre, RCT, moderate hospitalized adults. RBV + SOF/DCV (n=24) Control (n=24)	Length of hospitalization SE: ICU admission, invasive mechanical ventilation, time to recovery (hospital discharge)	Daclatasvir/Sofosbuvir + RBV vs control, median hospitalization duration 6d, vs 6d, (p= 0.398), number of ICU admissions similar (0 versus 4, p= 0.109), number of death similar0 vs 3, p= 0.234), Increased cumulative recovery incidence (Gray's P= 0.033)
Triazavirin (TZV)			
Author/date	**Study design/ number of participants (n)**	**Clinical outcome measures/primary endpoints**	**Main results**
Wu *et al.* 2020 [46]	Double-blind RCT in hospitalized adult patients TZV (n= 26) Placebo (n=26)	Time to clinical improvement (cough, oxygen saturation, respiratory rate, normal body temperature, and absorption of pulmonary infection by chest CT (28d)	TZV vs placebo, no differences in clinical improvement time (median, 7d vs. 12d; RR= 2.0; 95% (CI), 0.7–5.6; p = 0.2), clinical improvement in 10 vs 6 patients (38.5% vs. 23.1%; RR, 2.1; 95% CI, 0.6-7.0; p = 0.2)
Nitazoxanide (NTZ)			
Author/date	**Study design/ number of participants (n)**	**Clinical outcome measures/primary endpoints**	**Main results**
Blum *et al.* 2021 [49]	Randomized, double-blind, phase 2 trial NTZ(n=25) Placebo(n=25)	Clinical and virological end-points and inflammatory biomarkers, five-point scale for disease severity	NTZ vs placebo, *In vitro* inhibition of SARS-CoV-2 infection was 90% with 0.5 µM, with no cytotoxicity, 2 patients died vs 6 in the placebo arm (p=NS), superior SSD (p<0001), shorter mean discharge time (6.6 vs 14 days, p=0.021), higher negative PCR (21d) (p=0.035), Less adverse events vs placebo (p=0.04)
Rossignol *et al.* 2021 [50]	Double-blind randomized multicentre, mild/moderate patients NTZ (n=184) Placebo (n= 195)	Reduced duration of symptoms SE: Progression to severe illness, hospitalization, and viral load	NTZ vs placebo, 85% reduction in progression to severe illness (1/184, [0.5%] vs 7/195, [3.6%]) (p=0.07), Progression to severe illness in 0.9% vs 5.6%, 79% reduction in hospitalization rate, (1/184 [0.5%] vs 5/195 [2.6%]), positive viral load proportions not reduced, well-tolerated

Silva *et al.* 2021 [51]	Single-blinded, RCT single, parallel-group, pilot study in mild/moderate patients NTZ (n= 33) Placebo (n= 13)	Viral eradication from respiratory tract (7d) SE: Viral load reduction from respiratory secretions (7d, 14d, 35d) tolerability (Adverse events)	NTZ vs placebo, both groups showed decrease in viral load between days 1 and 7, (F = 63.053; p< 0.001) Reduction in viral load ≥ 35%, vs 15.4% in placebo, (32.4%, 95% CI; 2.1, 62.8) (t = 2.178; (p = 0.037), significant difference vs placebo
Rocco et al. 2020 [52]	Multicentre, double-blind, RCT on adult patients NTZ 5 day (n=194) Placebo (n=198)	Complete resolution of fatigue, fever, and dry cough (5d) SE: Hospitalization, serum biomarkers of inflammation, laboratory tests, and viral load	NTZ vs placebo, negative swabs in 29.9% vs 18.2% (p=0.009), higher viral load reduction, 55% vs 45% (p=0.013), other secondary outcomes not significant, no serious side effects
Novaferon (Nova)			
Author/date	**Study design/ number of participants (n)**	**Clinical outcome measures/primary endpoints**	**Main results**
Zheng *et al.* 2020 [53]	Parallel-group, open-label, RCT Nova (n=30) Nova + LPV/r (n=30) LPV/r (n=29)	SARS-CoV-2 clearance rates (6d) SE: Time to viral clearance	Nova treatment prevented viral infection (EC50 = 0.10 ng/ml) and inhibited viral replication in vitro, (EC50 = 1.02 ng/ml), Significantly higher viral clearance (6d) in Nova and combination vs LPV/r (50.0% vs. 24.1%, p = 0.0400, and 60.0% vs. 24.1%, p=0.0053), 3-day reduction in median time to viral clearance and in combination group vs LPV/r alone
Darunavir/cobicistat (DRV/c)			
Author/date	**Study design/ number of participants (n)**	**Clinical outcome measures/primary endpoints**	**Main results**
Chen *et al.* 2020 [55]	Single-centre, randomized, open-label trial on mild patients DRV/c + IFN-a (n=15) IFN-a (n=15)	Viral clearance rate of oropharyngeal swabs (7d)	DRV/c vs control, proportion of negative swabs (7d) 46.7% vs 60.0% (p =0.72) Viral clearance rate (3d) 20% in both groups, increasing to 26.7% and 20% (5d), well-tolerated
Milic *et al.* 2021 [56]	Observational retrospective study DRV/c (n=115) Control (n=158)	Reduced respiratory support, hospitalization time, mortality, and a composite of invasive mechanical ventilation	DRV/c vs control, similar clinical improvement and hospitalization NB. Significantly higher mortality rates in treatment groups vs control, serious adverse effects
Camostat mesylate			
Author/date	**Study design/ number of participants (n)**	**Clinical outcome measures/primary endpoints**	**Main results**
Gunst *et al.* 2021 [58]	A double-blind, randomized, placebo-controlled multicentre		Camostat vs control, similar time to clinical improvement, not statistically significant, (p = 0.31),

	study on hospitalized patients Camostat(n=137) Placebo(n=68)	the hazard ratio for mortality between the two groups was 0.82 (95% CI, 0.24 to 2.79; P = 0.75) and median time for a change in viral load from baseline to day 5 was -0·22 log10 copies/mL (p <0.05) and -0.82 log10 (p <0.05), no significant difference was seen in any of these parameters

Legend: **RBV**: ribavirin; **SE**: secondary endpoint; **RT-PCR**: reverse transcriptase-polymerase chain reaction; **SOF/DCV**: sofosbuvir/daclatasvir; **TZV**: triazavirin; **CI**: confidence interval; **RR**: risk ratio; **NTZ**: nitazoxanide; **SSD**: sum of squared deviations; **Nova**: novaferon

Neutralizing antibodies

Neutralizing monoclonal antibodies, including antibody cocktails, were investigated in a total of 1 178 patients, and these clinical trials are summarized in **Table 6**.

Bamlanivimab (LY-CoV555 or LY3819253) and etesivimab (LY-CoV016 or LY3832479) are monoclonal antibodies that neutralize the S-protein of SARS-CoV-2. They bind to different epitopes and are used concurrently to circumvent resistant variant strains that have mutated epitopes [62]. Currently, ongoing studies show promise, with bamlanivimab at a dose of 2 800mg showing an acceleration of viral load decline [63]. Evidence suggests that bamlanivimab with etesivimab is more effective than bamlanivimab monotherapy [62], which shows some effectiveness in reducing viral load and hospitalization [64], and reduced hospitalization significantly in real-world cases [65].

REGN-CoV-2 is an antibody cocktail consisting of 2 neutralizing human IgG1 antibodies, casirivimab and imdevimab that inhibit SARS-CoV-2 S-protein receptor binding. *In vivo* studies in rhesus macaques and hamsters indicated that this antibody cocktail has the potential to reduce viral loads in the lower as well as upper airway and provide both prevention and treatment for COVID-19 [66]. Casirivimab-imdevimab showed some efficacy, although the evidence is limited, and was associated with a greater reduction in viral load, especially in patients who did not yet have an activated immune system [67]. This antibody cocktail approach is new, with limited results, although there is currently another clinical trial underway (NCT04452318).

CT-P59 is a neutralizing antibody that blocks spike protein binding to ACE-2 receptors, with efficacy against various isolates of SARS-CoV-2. This neutralizing antibody shows some efficacy *in vitro* in decreasing viral loads of various SARS-CoV-2 isolates, e.g. South-African and a Korean, as well as the wild type of the virus [68, 69].

CT-P53 showed significantly inhibited viral replication *in vivo* [69] and a clinical study involving approximately 200 patients indicated that this agent increases viral clearance and decreases time to negative conversion as well as hospitalization [70]. More studies on this neutralizing antibody are necessary, but thus far the evidence looks promising.

It is also worth noting that there are other neutralizing antibodies that have shown potential in inhibiting SARS-CoV-2 and these currently target spike protein binding [71]. BRII-196, BRII-198, SCTA01, and Ty027 are anti-virus monoclonal antibodies currently undergoing phase 1 clinical trials [72]. The current phase 3 clinical trials include antibodies such as sotrovimab, regdanvimab, and TY027 [71].

Table 6. neutralizing monoclonal antibodies against SARS-CoV-2

Bamlanivimab/etesevimab (Bam/Ete) in COVID-19			
Author/date	**Study design/ number of participants (n)**	**Clinical outcome measures/primary endpoints**	**Main results**
Gottlieb *et al.* 2021 [62]	The BLAZE-1 study, randomized phase 2/3 trial, mild/moderate patients Bam 700mg (n=101) Bam 2800mg (n=107) Bam 7000mg (n=101) Bam/Ete 2800 mg each (n=112)	Change in log viral load (11d) SE: 3 Other viral load measures, 5 symptom measures and 1 clinical outcome measure [hospitalization,	Bam/Ete vs placebo, log viral load difference = –0.57 (11d) (95%CI, –1.00 to –0.14; p =0.01) (statistically significant), bam 700 mg was 0.09 (95%CI, –0.35-0.52; p =0.69), for bam 2800mg was –0.27 (95%CI, –0.71-0.16; p=0.21), for bam 7000mg was 0.31 (95%CI, –0.13-0.76; p=0.16) (NS),

	Placebo (n=156)	ED visits and/or death (29d)]	statistically significant differences between each group vs placebo in 10/84 points of secondary outcomes, hospitalization/ED visits 0.9% vs 5.8% statistically significant change from baseline (29d)
Lundgren *et al*. 2021 [73]	Randomized, double-blind trial, hospitalized patients Bam + RDV (n=163) Placebo + RDV (n=151)	Sustained recovery after 90 days, two ordinal outcomes (5d)	Bam vs placebo, 50% vs 54% fell in one of two most favourable categories of the pulmonary outcome on a 7-point ordinal scale (5d), overall OR of falling in a more favorable category was 0.85 (95% CI, 0.56 to 1.29; p =0.45), similar PEs (19% vs 14%; OR, 1.56; 95% CI, 0.78-3.10; p =0.20), sustained recovery rate ratio was 1.06 (95% CI, 0.77 to 1.47)
Chen *et al*. 2021 [63]	Ongoing, double-blind, phase 2 RCT, mild/moderate outpatients Bam 700mg (n=101) Bam 2800mg (n=107) Bam 7000mg (n=101) Placebo (n=143)	Change from baseline in viral load (11d)	Bam 2800 mg vs placebo, difference in a decrease from baseline in viral load −0.53 (95% CI, −0.98 to −0.08; p= 0.02) and viral load lower by a factor of 3.4 (Only dose with a statistically significant decrease), slightly lower severity of symptoms (2-6d), hospitalization 1.6% vs 6.3%
Dougan *et al*. [64]	Phase 3 RCT, mild/moderate patients Bam/ete (n=518) Placebo (n=517)	Overall clinical status (hospitalization and death)	Bam/ete vs placebo, Lower hospitalization (absolute risk difference, −4.8 percentage points; 95% CI, −7.4 to −2.3; relative risk difference, 70%; p<0.001), Significant reduction in log viral load, (difference from placebo in the change from baseline, −1.20; 95% CI, −1.46 to −0.94; p<0.001)
Casirivimab/imdevimab (REGN-COV2)			
Author/date	**Study design/ number of participants (n)**	**Clinical outcome measures/primary endpoints**	**Main results**
Weinreich *et al*. 2021 [67]	Ongoing, double-blind, phase 1–3 RCT, non-hospitalized patients REGN-COV2 2.4g (n= 92) REGN-COV2 8.0g (n=90) Placebo (n=93)	Time-weighted average change in viral load from baseline (7d) SE: Change in viral load from baseline to various days	REGN-COV-2 vs placebo, least-squares mean difference in primary endpoint was −0.56 log10 copies/ml (95% CI, −1.02 to −0.11) in serum negative patients and −0.41 log10 copies/ml (95% CI, −0.71 to −0.10) in the overall population, 3% vs 6%of patients reported at least 1 medical visit, in serum antibody negative patients, 6% vs 15% (difference, −9 percentage points; 95% CI, −29-11)
CT-P59 in COVID-19			
Author/date	**Study design/ number of participants (n)**	**Clinical outcome measures/primary endpoints**	**Main results**

Sik eom *et al.* 2021 [70]	Phase 2/3 double-blind RCT, mild/moderate outpatients. CT-p50 40mg/kg (n=101) CT-p50 80mg/kg (n=103) Placebo (n=103)	Time to negative conversion, nasopharyngeal swab (28d), clinical recovery (14d)	CT-P59 40mg/kg vs 80mg/kg vs placebo, median time to negative conversion, 12.8d (9.00–12.84) vs 11.9d (8.94-12.91) vs 12.9d (12.75–13.99), (95% CI), median time to recovery, 5.4d (3.97-6.78) vs 6.2d (5.53-7.85) vs 8.8d (6.72-11.73), lower hospitalization or oxygen (4.0% [1.6–9.7%]) vs (4.9% [2.1–10.9%]) vs (8.7% [4.7–15.8%), corresponding improvement rate ratios (95% CI) were 1.346 (1.001-1.810; p= 0.048), 1.215 (0.90-1.63; p= 0.198), and 1.275 (0.99-1.65; p=0.063), clinical recovery ratios (95% CIs) were 1.562 (1.11-2.20; p=0.010), 1.429 (1.02-2.01; p= 0.039), and 1.489 (1.11-2.01; p= 0.008), well tolerated.

Legend: **Bam/ete**: bamlanivimab/etesevimab

CONCLUSION

Currently, the monoclonal antibodies, sotrovimab, bamlanivimab/etesevimab and casirivimab/imdevimab reduce viral loads and have been granted FDA emergency use authorization for the treatment of mild-to-moderate COVID-19 in high risk adults and pediatric patients [74], Numerous other neutralizing antibodies are under investigation, and it is hoped that positive results will follow. To date, the antiviral, remdesivir, is the only FDA-approved antiviral agent for severe COVID-19. Newer evidence, including the WHO SOLIDARITY trial, indicates that monotherapy does not show significant efficacy, especially in reducing mortality. There is, however, some evidence of its efficacy in reducing recovery time in patients receiving oxygen therapy. There are several encouraging additional antiviral candidates that currently show potential efficacy against SARS-CoV-2. The most notable of these include favipiravir (increased viral clearance), sofosbuvir/daclatasvir (reduced hospitalization time, reduced mortality rates, significantly increased clinical recovery), and nitazoxanide (reduced viral loads, reduced hospitalization and disease progression). These warrant further clinical investigation. In addition, novaferon and nafamostat-mesilate may prove to be useful candidates for treating COVID-19, but more investigations are required to confirm their potential efficacy.

ACKNOWLEDGMENTS : The authors wish to acknowledge the Department of Pharmacology, University of Pretoria.

CONFLICT OF INTEREST : None

FINANCIAL SUPPORT : None

ETHICS STATEMENT : None

REFERENCES

1. Shereen MA, Khan S, Kazmi A, Bashir N, Siddiquea R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;24:91-8. doi:10.1016/j.jare.2020.03.005.
2. Dongyuan W, Zigang L, Yihui L. An overview of the safety, clinical application and antiviral research of the COVID-19 therapeutics. J Infect Public Health. 2020;13(10):1405-14. doi:10.1016/j.jiph.2020.07.004.
3. Eltayeb LB. An update about Coronaviruses with Emphasis on Newly Emerged COVID 19. J Biochem Technol. 2020;11(3):14-20.
4. Rahman AA, Khoso MH, Shaikh Z, Malik E, Siyal FJ, Rahoojo A, et al. Myths and realities: A novel study on COVID-19 among the medical students of Rural university of Sindh, Pakistan. Arch Pharm Pract. 2021;12(1):16-20.
5. Guarner J. Three emerging coronaviruses in two decades: the story of SARS, MERS, and now COVID-19. Am J Clin Pathol. 2020;153(4):420-1. doi:10.1093/ajcp/aqaa029.

6. Zaki N, Mohamed EA. The estimations of the COVID-19 incubation period: a systematic review of the literature. medRxiv. 2020. doi:10.1101/2020.05.20.20108340.
7. Jamshaid H, Zahid F, ud Din I, Zeb A, Choi HG, Khan GM, et al. Diagnostic and treatment strategies for COVID-19. AAPS Pharm Sci Tech. 2020;21(6):1-4. doi:10.1208/s12249-020-01756-3.
8. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433. doi:10.1016/j.jaut.2020.102433.
9. Hosseini A, Hashemi V, Shomali N, Asghari F, Gharibi T, Akbari M, et al. Innate and adaptive immune responses against coronavirus. Biomed Pharmacother. 2020;132:110859.
10. Du SQ, Yuan W. Mathematical modeling of interaction between innate and adaptive immune responses in COVID-19 and implications for viral pathogenesis. J Med Virol. 2020;92(9):1615-28. doi:10.1002/jmv.25866.
11. Li C, Xu BH. The viral, epidemiologic, clinical characteristics and potential therapy options for COVID-19: a review. Eur Rev Med Pharmacol Sci. 2020;24(8):4576-84. doi:10.26355/eurrev_202004_21044.
12. Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: structure, biology, and structure-based therapeutics development. Front Cell Infect Microbiol. 2020;10:724. doi:10.3389/FCIMB.2020.587269.
13. Simonis A, Theobald SJ, Fätkenheuer G, Rybniker J, Malin JJ. A comparative analysis of remdesivir and other repurposed antivirals against SARS-CoV-2. EMBO Mol Med. 2021;13(1):e13105. doi:10.15252/emmm.202013105.
14. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020;19(3):149-50. doi:10.1038/d41573-020-00016-0.
15. van Oosterhout C, Hall N, Ly H, Tyler KM. COVID-19 evolution during the pandemic–Implications of new SARS-CoV-2 variants on disease control and public health policies. Virulence. 2021;12(1):507-8. doi:10.1080/21505594.2021.1877066.
16. Centers for Disease Control and Prevention. Science Brief: Emerging SARS-CoV-2 Variants | CDC." Available from: https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html (accessed Mar. 09, 2021).
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(10236):1569-78. doi:10.1016/S0140-6736(20)31022-9.
18. 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(19):1813-26. doi:10.1056/nejmoa2007764.
19. Spinner CD, Gottlieb RL, Criner GJ, López JR, Cattelan AM, Viladomiu AS, 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(11):1048-57. doi:10.1001/jama.2020.16349.
20. Goldman JD, Lye DC, 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(19):1827-37. doi:10.1056/nejmoa2015301.
21. 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(9):795-807. doi:10.1056/nejmoa2031994.
22. Mahajan L, AP Singh G. Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study. Indian J Anaesth. 2021;65(13):S41-S6. doi:10.4103/ija.IJA_149_21.
23. Barratt-Due A, Olsen IC, Henriksen KN, Kåsine T, Lund-Johansen F, Hoel H, et al. Evaluation of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19 Patients: Results from the NOR-Solidarity Randomised Trial. SSRN Electron J. 2021. doi:10.2139/ssrn.3774182.
24. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19: interim WHO Solidarity Trial Results. N Engl J Med. 2020;384(6):497-511. doi:10.1056/nejmoa2023184.
25. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering. 2020;6(10):1192-8. doi:10.1016/j.eng.2020.03.007.
26. Dabbous HM, Abd-Elsalam S, El-Sayed MH, Sherief AF, Ebeid FF, Abd El Ghafar MS, et al. Efficacy of favipiravir in COVID-19 treatment: a multi-center randomized study. Arch Virol. 2021;166(3):949-54. doi:10.1007/s00705-021-04956-9.

27. Zhao H, Zhang C, Zhu Q, Chen X, Chen G, Sun W, et al. Favipiravir in the treatment of patients with SARS-CoV-2 RNA recurrent positive after discharge: A multicenter, open-label, randomized trial. Int Immunopharmacol. 2021;97:107702. doi:10.1016/j.intimp.2021.107702.
28. 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. doi:10.1016/j.ijid.2020.11.142.
29. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv. 2020. doi:10.1101/2020.03.17.20037432.
30. 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. doi:10.1016/j.ijid.2020.11.008.
31. 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(11):3366-72. doi:10.1093/jac/dkaa331.
32. Yadollahzadeh M, Eskandari M, Roham M, Zamani F, Laali A, Kalantari S, et al. Evaluation of Sovodak (Sofosbuvir/Daclatasvir) Treatment Outcome in COVID-19 Patient's Compared with Kaletra (Lopinavir/ritonavir): a Randomized Clinical Trial. 2021. doi:10.21203/rs.3.rs-257762/v1.
33. Yakoot M, Eysa B, Gouda E, Hill A, Helmy SA, Elsayed MR, et al. Efficacy and safety of sofosbuvir/daclatasvir in the treatment of COVID-19: a randomized, controlled study. SSRN Electron J. 2020. doi:10.2139/ssrn.3705289.
34. Alavi-moghaddam M, Haghighi M, Sabaghian T, Soroureddin Z, Chaboki BG. Safety and Efficacy of Sofosbuvir in Hospitalized Adult Patients with SARS-CoV-2: A Preliminary Report. Available at SSRN 3790463. 2021. doi:10.2139/ssrn.3790463.
35. 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(11):3379-85. doi:10.1093/jac/dkaa334.
36. 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(3):753-7. doi:10.1093/jac/dkaa501.
37. Choy KT, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KP, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res. 2020;178:104786. doi:10.1016/J.ANTIVIRAL.2020.104786.
38. 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.
39. 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. 2020;1(1):105-13. doi:10.1016/j.medj.2020.04.001.
40. Reis G, Silva EA, Silva DC, Thabane L, Singh G, Park JJ, 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(4):e216468. doi:10.1001/jamanetworkopen.2021.6468.
41. 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(1):69-75. doi:10.1016/j.jcv.2004.03.003.
42. Barnard DL, Day CW, Bailey K, Heiner M, Montgomery R, Lauridsen L, et al. Enhancement of the infectivity of SARS-CoV in BALB/c mice by IMP dehydrogenase inhibitors, including ribavirin. Antiviral Res. 2006;71(1):53-63. doi:10.1016/j.antiviral.2006.03.001.
43. Tong S, Su Y, Yu Y, Wu C, Chen J, Wang S, et al. Ribavirin therapy for severe COVID-19: a retrospective cohort study. J Antimicrob Agents. 2020;56(3):106114. doi:10.1016/j.ijantimicag.2020.106114.
44. Huang YQ, Tang SQ, Xu XL, Zeng YM, He XQ, Li Y, et al. No statistically apparent difference in antiviral effectiveness observed among ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha, and

ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate coronavirus disease 2019: results of a randomized, open-labeled prospective study. Front Pharmacol. 2020;11:1071. doi:10.3389/fphar.2020.01071.

45. 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(11):3373-8. doi:10.1093/jac/dkaa332.
46. Wu X, Yu K, Wang Y, Xu W, Ma H, Hou Y, et al. Efficacy and safety of triazavirin therapy for coronavirus disease 2019: a pilot randomized controlled trial. Engineering. 2020;6(10):1185-91. doi:10.1016/j.eng.2020.08.011.
47. Malík I, Čižmárik J, Kováč G, Pecháčová M, Hudecová L. Triazavirin might be the new hope to fight Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Ceska Slov Farm. 2021;70(1):18-25.
48. Lythgoe MP, Middleton P. Ongoing clinical trials for the management of the COVID-19 pandemic. Trends Pharmacol Sci. 2020;41(6):363-82. doi:10.1016/j.tips.2020.03.006.
49. Blum VF, Cimerman S, Hunter JR, Tierno P, Lacerda A, Soeiro A, et al. Nitazoxanide In Vitro Efficacy Against SARS CoV-2 and In Vivo Superiority to Placebo to Treat Moderate COVID-19–A Phase 2 Randomized Double-Blind Clinical Trial. SSRN Electron J. 2021. doi:10.2139/ssrn.3763773.
50. Rossignol JF, Bardin MC, Oaks JB, Bostick BG, Vora KN, Fulgencio J, et al. Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization. medRxiv. 2021. doi:10.1101/2021.04.19.21255441.
51. Silva M, Espejo A, Pereyra ML, Lynch M, Thompson M, Taconelli H, et al. Efficacy of Nitazoxanide in reducing the viral load in COVID-19 patients. Randomized, placebo-controlled, single-blinded, parallel group, pilot study. medRxiv. 2021. doi:10.1101/2021.03.03.21252509.
52. Rocco PR, Silva PL, Cruz FF, Melo-Junior MA, Tierno PF, Moura MA, et al. Early use of nitazoxanide in mild Covid-19 disease: randomised, placebo-controlled trial. Eur Respir J. 2021;58(1):2003725. doi:10.1183/13993003.03725-2020.
53. Zheng F, Zhou Y, Zhou Z, Ye F, Huang B, Huang Y, et al. SARS-CoV-2 clearance in COVID-19 patients with Novaferon treatment: A randomized, open-label, parallel-group trial. Int J Infect Dis. 2020;99:84-91. doi 10.1016/j.ijid.2020.07.053.
54. De Meyer S, Bojkova D, Cinatl J, Van Damme E, Buyck C, Van Loock M, et al. Lack of antiviral activity of darunavir against SARS-CoV-2. Elsevier Enhanc Reader. 2020;97:7-10. Available from: https://reader.elsevier.com/reader/sd/pii/S1201971220303921?token=E715C3253203F90E4F6D421915B83EE65CE9BB2265AD5DA2D04BA7DCD4193E2EA91EEA5685452349FA826A42B0C78460&originRegion=eu-west-1&originCreation=20210524131009 (accessed May 24, 2021).
55. 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(7). doi:10.1093/ofid/ofaa241.
56. Milic J, Novella A, Meschiari M, Menozzi M, Santoro A, Bedini A, et al. Darunavir/cobicistat is associated with negative outcomes in HIV-negative patients with severe COVID-19 pneumonia. AIDS Res Hum Retroviruses. 2021;37(4):283-91. doi:10.1089/aid.2020.0305.
57. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020;181(2):271-80. doi:10.1016/j.cell.2020.02.052.
58. Gunst JD, Staerke NB, Pahus MH, Kristensen LH, Bodilsen J, Lohse N, et al. Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial. EClinicalMedicine. 2021;35:100849. doi:10.1016/j.eclinm.2021.100849.
59. Hoffmann M, Schroeder S, Kleine-Weber H, Müller MA, Drosten C, Pöhlmann S. Nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. Antimicrob Agents Chemother. 2020;64(6):e00754-20. doi:10.1128/AAC.00754-20.
60. Jang S, Rhee JY. Three cases of treatment with nafamostat in elderly patients with COVID-19 pneumonia who need oxygen therapy. Int J Infect Dis. 2020;96:500-2. doi:10.1016/j.ijid.2020.05.072.
61. Search results for Nafamostat - Clinical Trials Registry - ICH GCP. Available from: https://ichgcp.net/clinical-trials-registry/research/list?intr=Nafamostat (accessed Jul. 26, 2021).

62. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, 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(7):632-44. doi:10.1001/jama.2021.0202.
63. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med. 2021;384(3):229-37. doi:10.1056/nejmoa2029849.
64. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. N Engl J Med. 2021;385(15):1382-92. doi:10.1056/NEJMOA2102685.
65. Kumar RN, Wu EL, Stosor V, Moore WJ, Achenbach C, Ison MG, et al. Real-world experience of bamlanivimab for COVID-19: a case-control study. Clin Infect Dis. 2022;74(1):24-31. doi:10.1093/cid/ciab305.
66. Baum A, Copin R, Ajithdoss D, Zhou A, Lanza K, Negron N, et al. REGN-COV2 antibody cocktail prevents and treats SARS-CoV-2 infection in rhesus macaques and hamsters. bioRxiv. 2020. doi:10.1101/2020.08.02.233320.
67. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med. 2021;384(3):238-51. doi:10.1056/nejmoa2035002.
68. Ryu DK, Song R, Kim M, Kim YI, Kim C, Kim JI, et al. Therapeutic effect of CT-P59 against SARS-CoV-2 South African variant. Biochem Biophys Res Commun. 2021;566:135-40. doi:10.1101/2021.04.27.441707.
69. Kim C, Ryu DK, Lee J, Kim YI, Seo JM, Kim YG, et al. A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein. Nat Commun. 2021;12(1):1-0. doi:10.1038/s41467-020-20602-5.
70. Eom JS, Ison M, Streinu-Cercel A, Săndulescu O, Preotescu LL, Kim YS, et al. Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebo-controlled trial in outpatients with mild-to-moderate SARS-CoV-2 infection. 2021. doi:10.21203/rs.3.rs-296518/v1.
71. Ning L, Abagna HB, Jiang Q, Liu S, Huang J. Development and application of therapeutic antibodies against COVID-19. Int J Biol Sci. 2021;17(6):1486-96. doi:10.7150/ijbs.59149.
72. Yang L, Liu W, Yu X, Wu M, Reichert JM, Ho M. COVID-19 antibody therapeutics tracker: a global online database of antibody therapeutics for the prevention and treatment of COVID-19. Antib Ther. 2020;3(3):205-12. doi:10.1093/ABT/TBAA020.
73. Lundgren JD, Grund B, Barkauskas CE, Holland TL, Gottlieb RL, Sandkovsky U, et al. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. N Engl J Med. 2021;384(10):905-14. doi:10.1056/nejmoa2033130.
74. Emergency Use Authorization | FDA. Available from: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization (accessed Jul. 22, 2021)