

Galaxy Publication

Evaluating the Clinical Efficacy of Antiviral Treatments for SARS-CoV-2

Angelique Welman^{1*}, Kim Outhoff¹

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

*E-mail ⊠ u18017046@tuks.co.za Received: 29 February 2021; Revised: 29 March 2021; Accepted: 05 April 2021

ABSTRACT

The virus that creates COVID-19, SARS-CoV-2, is highly contagious and typically replicates in the upper and lower respiratory tract to cause atypical pneumonia in humans. The gastrointestinal and cardiovascular tissues that contain its primary binding receptor, ACE2, may also be infected. A variety of therapeutic approaches have been investigated and modified to reduce the potentially dangerous clinical consequences of the COVID-19 pandemic. However, there isn't a proven cure for this illness at the moment. Clinical reports of the potential effectiveness of anti-SARS-CoV-2 antiviral drugs in reducing viral load, mechanical ventilation, recovery time, case fatality rates, and length of hospitalization in COVID-19 patients were reviewed in this literature review. Neutralizing antibodies such as casirivimab/imdevimab, bamlanivimab/etesevimab, and CT-P59 are clinically effective, particularly in reducing SARS-CoV-2 viral loads and reducing hospitalization and mortality; antiviral drugs such as sofosbuvir/daclatasvir, nitazoxanide, and favipiravir may be effective; and remdesivir, an antiviral approved by the FDA for severe disease, has suboptimal effect. Further studies of novaferon and nafamostat-mesylate are needed to confirm the promising findings. In conclusion, a range of antiviral strategies, such as remdesivir and neutralizing antibodies, may help reduce the impact of the virus, even though effective treatments for COVID-19 remain elusive. Even though vaccinations can prevent COVID-19, very few people worldwide have received it. Therefore, studies on anti-SARS-CoV-2 therapy must continue.

Keywords: COVID-19, Bamlanivimab/etesevimab, Remdesivir, SARS-CoV-2, Neutralizing antibodies

How to Cite This Article: Welman A, Outhoff K. Evaluating the Clinical Efficacy of Antiviral Treatments for SARS-CoV-2. Pharm Sci Drug Des. 2021;1:10-26. https://doi.org/10.51847/WyyopUKUKF

Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2) is a virus that creates ARDS (acute respiratory syndrome) and is similar to bat viruses. It first surfaced in Wuhan, China, in December 2019. SARS-CoV-2 most possibly originated in bats, mutated in a psychic species, and then went on to infect people [1-3]. The virus spreads swiftly through aerosolized and droplet particles, with an estimated median and mean incubation time of 5.01 and 7.8 days, respectively, ranging from 0 to 14 days [1, 4-6]. In addition to gastrointestinal symptoms or upper respiratory tract, infected people may exhibit fever, taste, dry cough, smell loss, and breath shortness. Mild sickness can develop into ARDS and moderate to severe pneumonia, which can occasionally be treated with mechanical ventilation [7-9]. The rate of case fatality for COVID-19 is between 2-3%. Depending on age and immune status, symptoms might appear anywhere from 6 to 41 days before death (14-day median) [7, 10].

Imaging investigations in people with severe COVID-19 reveal alveolar destruction that is consistent with the production of hyaline membranes, severe pneumonia, and acute respiratory discomfort syndrome [9, 10]. Additionally, inflammation high levels are visible in the alveolar wall, pneumocyte shedding, and neutrophil intraalveolar inflammatory infiltrates, all of which indicate secondary bacterial infection [9, 10]. Additionally, acute heart damage and potentially fatal grand-glass opacities can be detected by CT scans [7].

Similar to MERS-CoV and SARS-CoV, SARS-CoV-2 is an unsegmented, RNA, positive feeling beta coronavirus. It possesses a transmembranous viral S (spike) fusion protein that is opinion to attach to the

gastrointestinal and lung epithelial cells' ACE2 (angiotensin-converting enzyme 2) receptors and, to a lesser degree, to AGTR2 (angiotensin II receptor type 2) [11, 12].

The S (Spike) protein is composed of three RBDs (receptor-binding domains); the subunit S1 undergoes a chainlike shapeshift before connecting with the ACE2 receptor in an "up" configuration. The subunit S2 links in a more constant "down" state when the S1 is removed. Heptad repeats 1 (HR1) and 2 interact to generate the six-helical bundle (6-HB) that makes up S2. The membrane of the viral cell fuses with the membrane of the host cell once 6-HB is formed, causing infection [11, 12].

The SARS-CoV-2 transmissibility depends on the linking affinity between ACE2 and the spike-protein ectodomain structure. SARS-CoV-2 has a 10 to 20 times greater binding affinity to ACE2 receptors than SARS-CoV, which increases the risk of human-to-human transition of COVID-19 [11].

Following host cellular entrance, SARS-CoV-2 RNA is released, transcription and replication are carried out utilizing the replicate-transcriptase complex, and protein cleavage occurs. The virus releases its particles into the host cell following the translation, assembly, packaging, and replication of its structural proteins.

It has been suggested that ACE2 inhibitors and ARBs function as possible antivirals against the virus since ACE-2 receptors in the alveolar epithelium are the primary target and pathogenic mechanism of SARS-CoV-2 infection. Recent evidence, however, indicates that using these medications to treat COVID-19 may have negative effects [11, 13]. Supportive therapy, such as mechanical ventilation or high-flow oxygen, is crucial for patients suffering from severe acute respiratory distress syndrome. Short-term glucocorticoid immunosuppressive medicine is utilized to treat severe ARDS and inflammation, which may be related to cytokine storm or hyperinflammation. Additionally, glucocorticoids may help with consequences such as acute renal and heart damage [11, 12]. This article, however, focuses on evaluating the data for recently identified antivirals and repurposed antiviral medications that combat additional RNA viruses [11]. These contain neutralizing antibodies of anti-SARS-CoV-2 that can prohibit the virus from adhering and penetrating host cells, as well as commercially validated nucleoside analogs that may decrease the synthesis of viral RNA using targeting RNA-associated with RNA polymerase [14]. Papain-like protease and protease inhibitors, which have shown some effect in treating SARS and MERS, may be helpful in the COVID-19 treatment [7, 14].

For COVID-19, there are currently no proven viable treatment alternatives. The Indian B.1.671.2 (delta), the Brasilian 501Y.V3 (gamma), the South African 501Y.V2 (beta), and UK 501Y.V1 (alpha) are among the new SARS-CoV-2 variants that have already surfaced [15, 16]. However, this study emphasizes assessing the data for newly discovered antivirals and repurposed antiviral drugs that fight other RNA viruses [11]. These contain neutralizing antibodies of anti-SARS-CoV-2 that can prohibit the virus from adhering and entering host cells, as well as commercially licensed nucleoside analogs that may decrease the synthesis of viral RNA using targeting RNA-depends RNA polymerase [14]. Protease inhibitors and papain-like protease, which have shown some effect in the treatment of MERS, may be useful in the COVID-19 treatment.

Materials and Methods

Study design

Utilizing the following search criteria, the published literature was searched utilizing search engines such as Google Scholar, Cochrane, Prospero, and Ovid databases to find all results of clinical trials looking at antivirals versus SARS-CoV-2: "protease inhibitors", "nucleoside analogs", "antivirals", "neutralizing antibodies", "safety and efficacy", "SARS-Co-V-2", and "treatment/therapeutic options" in "COVID-19".

A search was also conducted for COVID-NMA, a systematic and living mapping evaluation of COVID-19 trials. By methodically searching the International Clinical Trials Registry Platform of WHO once a week, this program finds randomized controlled trials (RCTs) that assess COVID-19 therapies and preventive measures.

Sample size and collection

Several databases were searched for articles. First, duplicates were eliminated after titles and abstracts were checked. We examined all full-text English-language publications of nonclinical and clinical studies of antiviral therapy for SARS-CoV-2 or COVID-19.

Data extraction was done on those who met the inclusion criteria. All of these clinical trials, which included openlabel and randomized controlled trials, were published and concentrated on treatment options that objective SARS-CoV-2 in adults. Only preclinical research that investigated medications not previously evaluated in clinical trials was considered. Articles discussing therapeutic options for symptomatic COVID-19 were not included. These included research on traditional Chinese medicine, ivermectin, colchicine, glucocorticoids, and repurposed antimalarials like hydroxychloroquine or chloroquine. Additionally, preclinical investigations of medications with clinical proof were not included, nor were any studies involving children or pregnant people. A diagram of PRISMA was utilized to outline the research flow.

The Cochrane Library's modified data extraction forms were used to extract data from the eligible studies. Antiviral efficacy according to study type (RCT, non-clinical, open-label, placebo arm), changes in viral loads, recovery time, antiviral mechanism of action, hospitalization and mechanical ventilation prevalence and time, and COVID-19 case fatality rate were among the summarised results.

These were presented as numbers, means, ranges, and percentages whenever feasible. These facts were combined and talked about. Overall, conclusions and findings were reached.

Results and Discussion

38 publications were evaluated following the application of the inclusion/exclusion criteria (Figure 1, Table 1). Ten antiviral agents, including remdesivir, favipiravir, ribavirin, sofosbuvir/daclatasvir, lopinavir/ritonavir, triazavirin, nitazoxanide, novaferon, darunavir/corbicistat, camostat-, gabexate-, and nafamostat-mesylate, as well as three neutralising antibody cocktails, including casirivimab/imdevimab (REGN-COV-2), bamlanivimab/etesivimab, and CT-P53, were included in these 39 clinical trials, which involved 9 311 people. These are covered in the section below.



Figure 1. Diagram of PRISMA

Remdesivir (RDV)

Antiviral RDV is a pre-medication that readily crosses cell membranes and transforms into RDV-TP (its active triphosphate form). RDV-TP functions as a substrate for viral replicates in RNA viruses, including SARS-CoV-2, and competes with endogenous adenosine triphosphate for incorporation into RNA strands. This promotes the delayed chain termination synthesis, which in turn prevents viral reproduction. It has been demonstrated to prevent

the Middle East Respiratory Syndrome and the development of the severe critical pneumonia syndrome coronavirus 2 [13, 17].

The effectiveness of RDV has been investigated in eight RCTs, such as the WHO's SOLIDARITY trial, with 4,829 patients (**Table 1**). While then, larger trials [18-21] challenged these results, early studies [17, 22-24] produced encouraging outcomes. RDV demonstrated promise in early trials, particularly in research by Wang *et al.* [17] and Beigel *et al.* [22]. Although it only became significant in the latter research of 541 patients, a reduction in the recovery period was noted in both investigations, particularly in oxygen-dependent patients. Because of these results, RDV was authorized for use in emergencies [13]. However, it should be mentioned that both studies had several drawbacks because of COVID-19 limits, such as inadequate sample sizes and one open-label design, which, in light of more recent findings, may explain the early studies' misleading results [17, 22].

The potential effectiveness of five-day RDV treatment was suggested by two trials, both of which were quite small in size (n = 397 and n = 396). These trials showed considerably better odds of clinical recovery when compared to 10-day treatment. Nonetheless, there was no statistically significant difference between 5- and 10-day therapy overall [23, 24].

RDV therapy did not demonstrate overall efficacy and had no discernible impact on death or the progression of the disease, according to the WHO's critical SOLIDARITY trial (n = 2743). There is enough evidence from this study and two other investigations, including a nor-solidarity experiment, to conclude that RDV is not very effective. Combining RDV with barcitinab resulted in some improvement, but this was not compelling [18-21].

Table 1. RDV therapy for COVID-19			
Reference	Study design/participants number	primary endpoints/Clinical outcome measures	Main findings
Wang <i>et al.</i> [17]	Multicentre RCT, double-blind, severe patients Placebo (n = 79) RDV (n = 158)	Clinical recovery time (28d), released from hospital	RDV versus Placebo, No longer waiting for clinical recovery (ratio of hazard 1.23 [95% CI 0.87–1.75]) and (ratio of hazard 1.52 [0.95–2.43) NS, treatment suspended early because of side impacts, 12% versus 5%
Beigel <i>et al.</i> [22]	International double-blind RCT, the adaptive COVID-19 therapy trial, hospitalized patients Placebo: (n = 521) RDV (n = 541)	Time of recovery	RDV versus placebo, A substantial decrease in the period of improvement (p < 0.001) is remarkable in complement oxygen people (RRR 1.47 [95% CI: 1.17–1.84]), non-considerable decrease in rates of mortality (14d) (P = 0.06)
Spinner <i>et al.</i> [23]	Moderate patients, RCT, phase three open-label Standard care (n = 200) 5-day RDV (n = 199) 10-day RDV (n = 197)	Clinical situation (11d) on 7-point sequential scale	RDV versus placebo, substantial enhancement in a clinical situation (11d) in the 5-day group (ratio of odds 1.65 [95% CI: 1.09–2.48, P = 0.02]), no difference in the 10-day group (P = 0.18 by the test of Wilcoxon rank sum)
Goldman <i>et</i> <i>al.</i> [24]	Open-label, RCT, hospitalized people, phase 3 RDV 10-day (n = 197) RDV 5-day (n = 200)	Clinical situation (14d) on 7-point sequential scale	10-day versus 5-day groups, clinical recovery of > 2 points, 64% versus 54%, alike dispensation in clinical situations (14d), (P = 0.14), The 10-day group had a considerably worse base clinical situation (P = 0.02)
Barratt-Due et al. [20]	Multi-country, Solidarity of NOR, adaptive randomized trial, open-label, hospitalized people. SoC (n = 87) HCQ (n = 52) RDV (n = 42)	Reception to ICU, in-hospital mortality, and mechanical ventilation initiation	, NS variations in the main endpoints

Welman and Outhoff, Evaluating the Clinical Efficacy of Antiviral Treatments for SARS-CoV-2

WHO Solidarity trial [21]	Trial of WHO solidarity Control (n = 4088) RDV (n = 2750)	In-hospital deaths	RDV versus control, Death in 301 of 2743 people versus 303 of 2708 people (ratio of rate, 0.95; 95% CI, 0.81-1.11; P = 0.50), no general definitive effect in other endpoints
Kalil <i>et al.</i> [18]	RCT, hospitalized people, Double-blind, barcitinab + RDV (n = 515) RDV (n = 518)	Improvement time SE: Clinical recovery (15d)	Composition versus RDV, Median improvement period 7d (95% CI, 6-8), versus 8d (ratio of rate for improvement, 1.16; 95% CI, 1.01-1.32 (P = 0.03), higher recovery odds in a clinical situation (15d) (ratio of odds, 1.3; 95% CI, 1.0-1.6), ventilated peoples' improvement period, 11d versus 18d (ratio of rate, 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), severe adverse impacts and fresh 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)-(-1.9); P = 0.003)
Mahajan <i>et</i> <i>al.</i> [19]	Moderate/severe patients, prospective randomized trial. SoC (n = 36) RDV (n = 34)	Clinical situation (14d), time to recovery, clinical death, and improvement	RDV versus SoC, no statistically remarkable difference in oxygen therapy, time to recovery, clinical situation, or mortality (P = 0.749)

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

Favipiravir (FPV)

A viral RdRp inhibitor, favipiravir (T-705) is an oral pyrazine formative. For instance, in influenza, the active triphosphate form acts as a nucleotide analog that initiates deadly viral mutagenesis via random point mutations and promotes chain termination by competing with ATP and GTP for RNA incorporation. Its antiviral action is extensive. In cell-based tests, favipiravir has revealed a poor effect in suppressing SARS-CoV-2 [13]. Nonetheless, In open-label clinical trials, FVP has shown a significant reduction in viral release [25-29]. **Table 2** provides a summary of the six clinical trials evaluating favipiravir therapy for COVID-19. The most significant results were from Zhao *et al.* [27], who discovered that FPV administration dramatically reduced several viral parameters. Evidence indicates that FPV has some effectiveness in lowering viral load, which is consistent with results by Cai *et al.* [25] and Udwadia *et al.* [28]. Additionally, it was shown that FPV was more effective than chloroquine (QC), however, this difference was not statistically remarkable [26]. There were no changes in the rate of clinical recovery when coupled with arbidol [29]. However, the shortcomings of each of these studies highlight the necessity of more comprehensive clinical studies and meticulously designed trials.

Table 2. FPV (Favipiravir) therapy for COVID-19				
Reference	Study design/participants number	primary endpoints/Clinical outcome measures	Main findings	
Cai <i>et al.</i> [25]	Non-randomized Trial, Open-label, LPV/r (n = 45) FPV (n = 35) (Both groups are composed of IFN-alpha 1b therapy)	Viral release time and chest CT recovery (14d)	FPV versus control, lower median viral release period, 4d (IQR: 2.5-9) versus 11d (IQR: 8-13), (P < 0.001), significant higher recovery in chest CT, 91.43% versus 62.22%, (P = 0.004)	
Dabbous <i>et</i> <i>al.</i> [26]	Interventional stage 2/3 RCT, multicenter, mild to moderate people CQ (n = 48) FPV (n = 48)	Rate of mortality and mechanical ventilation	FPV versus CQ, 1 death (2.3%), versus 2 (4.2%) (P = 1.00), lower hospitalization (P = 0.06), not significantly related to mortality (P = 0.615), no people on mechanical ventilation in FPV (P = 0.129)	

Chen <i>et al.</i> [29]	Open-label, prospective, RCT, multicentre Arbido 1 (n = 120) FPV (n = 116)	Rate of clinical improvement (7d) SE: Time of fever, time to cough relief, and auxiliary oxygen treatment/non-aggressive mechanical ventilation	FPV versus arbidol, rate of clinical improvement of 71.43% versus 55.86% (P = 0.0199), a significantly shorter period of fever and cough relief decrease (both P < 0.001), alike non-invasive mechanical ventilation and auxiliary oxygen treatment (both P > 0.05), well-endured.
Zhao <i>et al.</i> [27]	SARS-CoV-2 RNA re- positive people, multicenter, RCT, open- label, Control (n = 19) FPV (n = 36)	Duration of getting twice consecutive negative RT- PCR findings (> 24 h apart) for SARS-CoV-2 in sputum and nasopharyngeal samples	FPV versus control, significant lower time of primary endpoint (median 17 versus 26 d); the ratio of hazard 2.1 (95% CI [1.1-4.0], P = 0.038), the enhanced ratio of virus shedding (80.6% [29/36] versus 52.6% [10/19], (P = 0.030, respectively), significantly reduce in CRP (P = 0.016), mild undesirable events
Udwadia <i>et</i> <i>al.</i> [28]	Randomized, phase 3 trial, mild/ moderate people, parallel-arm, open-label, multicenter Contro 1 (n = 75) FPV (n = 75)	Duration of clinical cure and duration of viral shedding cessation	FPV versus control, median stop of viral pouring time of 5d (95% CI: 4d, 7d) versus 7d (95% CI: 5d, 8d) (P = 0.129), median period to clinical treatment, 3d (95% CI: 3d, 4d) versus 5d (95% CI: 4d, 6d) (P = 0.030), side impacts 36% versus 8%.
Khamis <i>et al.</i> [30]	Open-label, moderate/severe hospitalized people, RCT HCQ (n = 45) FPV + IFN-beta (n = 44)	Hospitalization, evacuation, and lower mortality (14d)	IFN-beta and FPV versus HCQ, no remarkable differences between the duration of hospitalization (7 versus 7d; P = 0.948), ICU transfer (18.2% versus 17.8%; P = 0.960), hospital release (65.9% overall 68.9%; P = 0.764), and total mortality (11.4% versus 13.3%; P = 0.778)

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

Sofosbuvir/daclatasvir (SOF/DCV)

An analog of a nucleotide called sofosbuvir suppresses the synthesis of positive sense RNA and is prescribed to treat hepatitis C virus infection. It binds to Main protease and RdRp to prevent their action, resulting in wide antiviral efficacy when coupled with daclatasvir [31].

Comparing this combination therapy to lopinavir/ritonavir (LPV/r) [32] revealed no statistically remarkable improvement in mortality or remission (**Table 3**). However, as compared to SoC (standard of care) control groups, SOF/DCV considerably boosted recovery rates [31, 33] and greatly decreased hospitalization [34, 35] in two small investigations. As a result, there is mounting evidence that the combination improves these outcomes, and more studies could clarify how it addresses COVID-19 [36].

Table 3. SOF/DCV	(Sofosbuvir/daclatasvir) therapy for COVID-19
------------------	-------------------------	------------------------

Reference	Study design/participants number	primary endpoints/Clinical outcome measures	Main findings
	Open lobel porollel	Time of hospital discharge	RBV versus SOF/DCV,
Eslami et al.	open-laber parallel	SE: side effects, ICU	median hospitalization in 9d versus 5d ($P < 0.01$),
[31]	U I d I DDV $(n = 27)$	duration, respiratory rate	33% mortality versus 6% ($P = 0.01$),
	RBV (n = 27)	laboratory values, and	Risk of relative death, 5.8% vs 0.17% (P = 0.02),
	SOF/DCV(II-55)	mortality	time of median recovery, 11d versus 6d ($P < 0.01$)
		The clinical recovery	SOF/DCV versus SoC, the enhanced ratio of
Yakoot <i>et al.</i> [33]	Parallel 2-arm, open-	proportion (14 and 21d),	cumulative clinical improvement at 21d, 91% (91%;
	label, RCT	oxygen saturation, respiratory	CI: 78.8%-96.4%) versus 76% (77.8%;63.7%-
	SOF/DCV (n = 44)	rate, during of viral	87.5%)),
	SoC $(n = 45)$	negativity, during of clinical	the statistically remarkable enhancement in clinical
		recovery, and mean clinical	recovery probability of nearly 1.6 times,

		situation changes on an 8-	enhanced effectiveness in the rate of case fatality,
		point sequential scale	mean severity of score of lung lesions, and a score of
		SE: Mechanical ventilation,	8-point ordinal scale; none of them were statistically
		undesirable events	remarkable,
			well-tolerated
	DCT Onen label	PE: Clinical improvement	SOF/DCV versus SoC,
	KCI, Open-label,	(within 14d) (oxygen	clinical improvement, 88% versus 67% ($P = 0.076$),
Sadeghi et al.	severe/moderate	saturation and normal fever)	lower hospitalization time [6 days (IQR 4-8) versus (8
[35]	adults, multicentre. $(n\Sigma_{2}C = 22)$	SE: All-reason mortality,	days (IQR 5-13)]; P = 0.029,
	(1150C - 55)	hospitalization duration,	Cumulative hospital release is remarkably higher
	(11SOF/DCV = 55)	mechanical ventilation,	(Gray's $P = 0.041$).
		discharge period.	No serious undesirable events
		Rate of clinical improvement	
	Randomized clinical	(normal respiration, body	SOF/DCV therapy: No remarkable differences in ICU,
Yadollahzadeh	trial	temperature, and oxygen	remission, death, and comorbidities.
<i>et al.</i> [32]	LPV/r (n = 54)	saturation).	Lower rate of hospital release than LPV/r ((95% CI =
	SOF/DCV (n = 58)	SE: Relative radiological	1.008-2.386; HR = 1.551 ; P = 0.046).
		report for progression of	Better finding by risk plot than LPV/r.
		lesion, recovery, and	
		mechanical ventilation.	
	In mild outpatients,	Symptom reduction after /-	SOF/DCV therapy: Both groups' base specifications
Roozbeh et al.	RCT, double-blind,	day follow-up.	were comparable, and there were no perceptible
[36]	HCQ $(n = 28)$	SE: appetite loss, fatigue,	variations in symptoms.
	SOF/DCV (n = 27)	hospital admission, and	The difference in nospitalization was not remarkable.
		dysphoea after 1-month	Fatigue decreased after 1-month follow-up, 16 people
	DI Q.	follow-up.	versus 2, $P < 0.001$.
	Phase 2 in	Clinical improvement	SOF therapy: Primary result obtained, 88.9% versus
A 1	nospitalized people,	(oxygen saturation and	33.3% in control (P < 0.001). Notably lower median
Alavi-	DCT	temperature of normal body).	hospitalization period versus control (10 days (IQR 5-
	RCI	SE: All-reason mortality in	12) versus 11.5 days (IQR 8.5-17.75); P = 0.016).
al. [34]	SOC (n - 30)	hospitalization, or discharge	All-reason mortality is 2% versus 13%, not
	SOF $(n = 27)$	within 14 days.	remarkable.

Legend: PE: primary endpoint

Lopinavir/ritonavir (LPV/r)

When taken in conjunction with HIV-1 treatment, these antiretroviral (ARV) protease inhibitors mainly cleave HIV polyproteins. The CYP 450 enzyme inhibitor ritonavir makes lopinavir more bioavailable [13]. Although Choy *et al.* [37] in vitro results were conflicting, LPV/r has exhibited effectiveness against SARS-CoV-2, as seen by decreased viral loads. Research indicates that there are no significant advantages to using LPV/r to treat COVID-19 (**Table 4**) [38-40]. This composition did not significantly lower hospitalization length, symptoms, or death rates than HCQ (hydroxychloroquine) or arbidol. Additionally, it revealed no advantages in terms of duration of clinical recovery, death, or hospitalization [38-40]. Most remarkably, there was no discernible clinical improvement with LPV/r use in the WHO SOLIDARITY study (n = 1.411) [21].

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

Reference	Study design/participants number	primary endpoints/Clinical outcome measures	Main findings
Cao <i>et al.</i> [38]	Open-label trial in hospitalized adults, RCT. LPV/r (n = 99) SoC (n =100)	Clinical recovery time (recovery of 2 points of a 7-point hospital discharge or ordinal scale).	LPV/r versus SoC, No remarkable differences in the period of clinical recovery (ratio of hazard, 1.24; 95% [CI], 0.90-1.72), alike mortality, 28d (19.2% versus 25.0%; difference, - 5.8% points; 95% CI, (-17.3)-(5.7)) duration of clinical recovery lower by 1 day (ratio of hazard, 1.39; 95% CI, 1.00-1.91), identifiable viral RNA at different time frames, GI undesirable events are more usual

Welman and Outhoff, Evaluating the Clinical Efficacy of Antiviral Treatments for SARS-CoV-2

Li <i>et al.</i> [39]	Mild/moderate people, exploratory RCT. LPV/r (n = 34) Placebo (n = 17) Arbido l (n = 35)	Rate of conversion of positive to negative viral nucleic acid. SE: clinical situation (antipyresis rate, cough resolution rate, rate of CT recovery (7 and 14d)	LPV/r versus arbidol versus placebo, primary endpoint alike between groups (P > 0.05), same secondary endpoints measurements (7d or 14d) (all P > 0.05), the clinical situation from moderate-severe in 23.5% of people, versus 8.6% versus 11.8%
Reis <i>et al.</i> [40]	Randomized trial LPV/r (n = 244) Placebo (n = 227) HCQ (n = 214)	Death and hospitalization (90d) SE: All-reason hospitalization, viral clearance, side impacts, and resolution of the symptom	LPV/r versus HCQ versus placebo, hospitalization, 5.7% versus 3.7% versus 4.8%, differences not statistically remarkable HCQ: ratio of hazard [HR], 0.76 [95% CI = 0.30-1.88]; LPV/r: HR, 1.16 [95% CI = 0.53-2.56], variation in viral release not statistically remarkable (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 [21]	WHO associated trial Control (n = 4088) LPV (n = 1411)	Mortality, ventilation, or hospitalization time	LPV versus control, Death in 148/1399 people versus 146/1372, No remarkable decrease in any endpoints

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

 Table 5 provides all miscellaneous agents' clinical research papers that include triazavirin, novaferon, nitazoxanide, ribavirin, camostat mesylate, and darunavir/cobicistat therapy.

Ribavirin (RBV)

An analog of guanosine, ribavirin, binds to RNA strands and prevents RNA production. It reduces GTP pools and has mutagenesis effects on viruses like influenza [13]. Despite showing antiviral action against coronaviruses in vitro, it appears to have little efficacy in treating COVID-19 [41]. In vivo, ribavirin demonstrated negligible to no efficacy in a trial involving ten SARS isolates, and it was not suggested as a potential medication to be tested clinically [42]. However, three studies evaluating the ribavirin effectiveness in severe COVID-19 people reported minimal clinical improvement when the drug was used as monotherapy [43], in composition with lopinavir/ritonavir [44], or with sofosbuvir/daclatasvir (**Table 5**) [45].

Triazavirin (TZV)

Since 2015, TZV has been sold in Russia. It prevents the production of viral ribonucleic acids and certain genomic segments replication [46]. Computational in silico research indicates that TZV interacts with non-structural 3-chymotrypsin-such as structural proteins and proteases in SARS-CoV-2, like S- and E-proteins. Its antiviral properties are likewise broad-spectrum. In humans, it has also demonstrated some linking affinity for ACE-2 [47]. However, no differences in time to clinical improvement were seen in a short double-blind RCT (**Table 5**) [46]. There is presently a second clinical trial on TZV (ChiCTR2000030001) [48].

Nitazoxanide (NTZ)

Although nitazoxanide possesses broad-spectrum antiviral qualities, it was initially utilized as an anti-protozoal. It disrupts host-regulated and interferon signaling pathways involved in viral replication. Each virus may have a different method. NTZ revealed promising effects in several metrics, including considerably lowering viral loads of SARS-CoV-2 [49-52] and immunological markers, in addition to 90% SARS-CoV-2 in vitro suppression (**Table 5**) [49]. Additionally, it has demonstrated potential in managing COVID-19 symptoms [51] and has been shown to help lower disease advance and hospitalization [48]. According to research, NTZ provides greater therapeutic advantages than a placebo, such as lowering viral loads, hospital stays, and recovery times [52].

Novaferon

Zheng *et al.* [53] studied the novaferon effect, a broad-spectrum antiviral drug utilized to treat the infection of chronic hepatitis B. Novaferon, a more powerful non-natural protein of human interferon alpha-2b subtypes, was

made by using an enhanced DNA shuffling approach. According to in vitro experiments, this drug suppressed viral infection and viral replication in cells. In a brief clinical trial, novaferon significantly increased viral clearance rates both alone and in combination with LPV/r, recommending its potential effect (**Table 5**) [53]. More study is recommended as a possible anti-SARS-CoV-2 agent.

Darunavir/cobicistat (DRV)

The HIV-1 protease is inhibited by darunavir, and its plasma half-life is prolonged by corbistat. For this reason, they are combined. In vitro, DRV did not exhibit any suppression of SARS-CoV-2 in contrast to RDV [54]. The effects of DRV/c have only been studied in two clinical trials, and neither of them showed any concrete evidence that DVR/c improved outcomes (**Table 5**) [55]. An exploratory retrospective study revealed that this combination was inefficient and that the ventilation and death rates were greater than those of controls, suggesting that it may be detrimental to treating hospitalized COVID-19 patients [56].

Camostat-, gabexate-, nafamostat-mesylate

By decreasing the priming of viral S-proteins, the synthetic protease inhibitors comastat, gabexate and nafamostat mesylate of epithelial TMPRSS2 may impede host cell entry [57, 58]. Compared to camostat and gabexate, nafamostat mesylate appears to have an almost 15-fold greater SARS-CoV-2 inhibitory efficacy, according to in vitro studies [59]. One clinical research suggested that camostat mesylate extended the duration of clinical recovery and deceased death, albeit the results were not statistically notable (**Table 5**). Nonetheless, the median alteration in a load of viral to day 5 increased noticeably [58]. Nonetheless, preclinical evidence recommends that nafamostat may be a more suitable option than camostat [59].

Three elderly people with severe COVID-19 pneumonia who were treated with nafamostat after hospitalization for 15 days improved their clinical status, according to a single case study [60]. Nafamostat's usage in COVID-19 may be supported by three clinical trials that are now assessing its effectiveness (NCT04418128, NCT04352400, and NCT04473053) [61].

Ribavirin (RBV)				
Reference	Study design/participants number	primary endpoints/Clinical outcome measures	Main findings	
Tong <i>et al.</i> [43]	severe patients, retrospective cohort study. Control (n = 71) RBV (n = 44)	Negative conversion time for SARS-CoV-2 RT-PCR SE: Rate of mortality	RBV versus control, 12.8 ± 4.1 versus 14.1 ± 3.5 days negative conversion period (P = 0.314), 17.1% deaths versus 24.6% (P = 0.475), similar undesirable events.	
Huang <i>et</i> <i>al.</i> [44]	The randomized, single-center, prospective trial, open-label. (n = 101) ratio = 1:1:1 (IFN-a + nRBV) (IFN-a + nLPV/r) (nRPV + IFN-a + nLPV/r)	The median variation in the interval to viral nucleic acid negativity, the ratio with nucleic acid negativity (14d), mortality (28d), undesirable events, ratio re-classified as severe	IFN-alpha + RBV versus LPV versus composition, median interval from base nucleic acid negativity, 13d versus 12d versus 15d (P = 0.23), ratio people with nucleic acid negativity (14d) (51.5%, versus 61.1%, and 46.9%) (P < 0.05), illness advance, 3.0% versus 5.6% and 6.3%, not remarkable, undesirable events notably higher in the composition group.	
Kasgari <i>et</i> al. [45]	Moderate hospitalized adults, single-center, RCT. Control (n = 24) SOF/DCV + RBV (n = 24)	Hospitalization period SE: invasive mechanical ventilation, duration of improvement (hospital release), ICU reception	$\begin{array}{l} \text{RBV + Daclatasvir/Sofosbuvir versus control,} \\ \text{median hospitalization time 6d, versus 6d (P = 0.398),} \\ \text{similar ICU perception number (0 versus 4, P = 0.109),} \\ \text{a similar number of deaths 0 versus 3 (P = 0.234),} \\ \text{enhanced cumulative improvement incidence} \\ & (\text{Gray's P= 0.033)} \end{array}$	
		Triazavirin (TZV)		

Table 5. Miscellaneous possible therapy for COVID-19

Reference	Study design/ participants number	primary endpoints/ Clinical outcome measures	Main findings
Wu <i>et al.</i> [46]	Double-blind RCT in hospitalized people Placebo (n = 26) TZV (n = 26)	Duration of clinical recovery (oxygen saturation, cough, normal body temperature, rate of respiratory, and pulmonary infection absorption using chest CT (28d)	TZV versus placebo, no differences in clinical recovery duration (median, 7d versus 12d; RR= 2.0; 95% (CI) = 0.7-5.6; P = 0.2), clinical recovery in 10 versus 6 people (38.5% versus 23.1%; 95% CI = 0.6-7.0; RR, 2.1; P = 0.2)
		Nitazoxanide (NTZ)	
Reference	Study design/ participants number	primary endpoints/ Clinical outcome measures	Main findings
Blum <i>et al.</i> [49]	Randomized, phase 2 trial, double-blind Placebo (n = 25) NTZ (n = 25)	Inflammatory biomarkers, virological and clinical end- points, and a five-point scale for disease severity	NTZ versus placebo, In vitro, infection of SARS-CoV-2 inhibition was 90% with 0.5 μ M, with no cytotoxicity, 2 people died versus 6 in the placebo arm (P = NS), lower mean release period (6.6 versus 14 days, P = 0.021), superior SSD (P < 0001), higher negative PCR (21d) (P = 0.035), low undesirable events versus placebo (P = 0.04)
Rossignol et al. [50]	Double-blind, mild/moderate patients, multicentre, randomized Placebo (n = 195) NTZ (n = 184)	Reduced symptoms duration SE: Progression to viral load, severe illness, and hospitalization	NTZ versus placebo, 85% decrease in advance to intense disease (1/184, [0.5%] versus 7/195, [3.6%]) (P = 0.07), advance to severe disease in 0.9% versus 5.6%, 79% decrease in the rate of hospitalization (1/184 [0.5%] versus 5/195 [2.6%]), positive viral load ratio not decreased, well-tolerated
Silva <i>et al.</i> [51]	A single-blinded, pilot research in moderate/mild people, parallel-group, RCT single Placebo (n = 13) NTZ (n = 33)	Viral deracination from the respiratory tract (7d) SE: Load of viral decrease from respiratory secretions (7d, 14d, 35d) tolerability (Undesirable events)	NTZ versus placebo, both groups revealed a reduction in load of viral between days one and seven (F = 63.053; P < 0.001) Decrease in load of viral \geq 35%, versus 15.4% in placebo (32.4%, 95% CI = 2.1, 62.8; t = 2.178; P = 0.037), remarkable difference versus placebo
Rocco et al. [52]	Multicentre, RCT on adult people, double-blind Placebo (n = 198) NTZ 5 days (n = 194)	Complete resolution of dry cough, fever, and fatigue (5d) SE: Viral load serum biomarkers, hospitalization, inflammation, and laboratory studies	NTZ versus placebo, negative swabs in 29.9% versus 18.2% (P = 0.009), higher load of viral decrease, 55% versus 45% (P = 0.013), other secondary finding not notable, no critical side impacts
		Novaferon (Nova)	
Reference	Study design/ participants number	primary endpoints/ Clinical outcome measures	Main findings
Zheng <i>et</i> <i>al.</i> [53]	RCT, Parallel-group, Nova, LPV/r (n = 29), open-label (n = 30) Nova + LPV/r (n = 30)	SARS-CoV-2 release rates (6d) SE: Period to viral release	Nova therapy inhibited the infection of viral $(EC_{50} = 0.10 \text{ ng/ml})$ and prevented viral reproduction in vitro $(EC_{50} = 1.02 \text{ ng/ml})$, notably higher viral release (6d) in Nova and composition versus LPV/r (50.0% versus 24.1%, P = 0.0400, and 60.0% versus 24.1%, P = 0.0053), 3-day decrease in the median duration of viral release and the composition group versus LPV/r alone

Darunavir/cobicistat (DRV/c)						
Reference	Study design/ participants number	primary endpoints/ Clinical outcome measures	Main findings			
Chen <i>et al.</i> [55]	Label trial on mild patients, single-center, open- randomized IFN-a (n = 15) DRV/c + IFN-a (n = 15)	Viral release rate of oropharyngeal swabs (7d)	DRV/c versus control, the negative swabs proportion (7d) is 46.7% versus 60.0% (P = 0.72) Rate viral release (3d) 20% in both groups, enhancing to 26.7% and 20% (5d), well-tolerated			
Milic <i>et al.</i> [56]	Observational retrospective research Control (n = 158) DRV/c (n = 115)	Decreased respiratory assistance, hospitalization duration, mortality, and an invasive mechanical ventilation composite	DRV/c versus control, alike clinical recovery and hospitalization NB. Notably higher rates of mortality in groups of treatment versus control, serious undesirable impacts			
		Camostat mesylate				
Reference	Study design/ participants number	C primary endpoints/ Clinical outcome measures	Main findings			
Gunst <i>et al.</i> [58]	A double-blind, placebo- controlled multicentre study on hospitalized patients, randomized Placebo(n = 68) Camostat(n = 137)	1	Camostat versus control, Similar time to clinical recovery, not statistically notable (P = 0.31), the ratio of hazard for mortality between the two groups was 0.82 (95% CI, 0.24 to 2.79; P = 0.75) and the median period for an alter in load of viral from base to day 5 was -0.82 log10 (P <0.05) and -0.22 log10 copies/mL (P < 0.05), no remarkable difference was reported in any of these parameters.			

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

Neutralizing antibodies

Table 6 summarises the clinical trials that looked into neutralizing monoclonal antibodies, such as antibody cocktails, in the sum of 1,178 individuals.

Monoclonal antibodies called etesivimab (LY3832479 or LY-CoV016) and bamlanivimab (LY3819253 or LY-CoV555) neutralize the SARS-CoV-2 S-protein. Because they attach to various epitopes, they are utilized together to circumvent resistant variant strains with modified epitopes [62]. According to current research, bamlanivimab at a 2,800 mg dose speeds up the viral load's decreases [63]. Studies reveal that etesivimab plus bamlanivimab is more efficient than bamlanivimab alone [62], which has been shown to have a moderately beneficial effect on reducing hospitalization and viral load [64] and to significantly reduce hospitalization in real-world situations [65].

Casirivimab and imdevimab, two neutralizing human IgG1 antibodies that prevent the S-protein receptor of SARS-CoV-2 binding, make up the antibody cocktail known as REGN-CoV-2. This antibody cocktail can lower viral loads in the upper and lower airways and prevent and treat COVID-19, according to in vivo investigations conducted in hamsters and rhesus macaques [66]. Casirivimab-imdevimab showed modest efficacy and was related to a greater decrease in viral load, especially in those without an activated immune system, despite the lack of data [67]. Although another clinical trial is presently in progress, this antibody cocktail technique is novel and has shown very modest outcomes (NCT04452318).

A neutralizing antibody called CT-P59 effectively inhibits spike protein linking to receptors of ACE-2 in a variety of SARS-CoV-2 isolates. In vitro, this neutralizing antibody exhibits modest effectiveness in reducing the viral loads of different SARS-CoV-2 isolates, including Korean and South African strains, and the virus's wild form [68, 69].

CT-P53 improves viral clearance and shortens the duration of negative conversion and hospitalization, according to clinical research involving more than 200 people [70]. Additionally, it showed a significant reduction of viral replication in vivo [69]. The evidence supporting this neutralizing antibody is promising thus far, but additional

research is needed. Other neutralizing antibodies that now target spike protein binding have shown potential in blocking SARS-CoV-2, so it's also crucial to keep that in mind [71]. The anti-virus monoclonal antibodies Ty027, SCTA01, BRII-196, and BRII-198 are now undergoing phase one clinical trials [72]. Phase three clinical trials are testing several antibodies, including regdanvimab, TY027, and sotrovimab [71].

Bamlanivimab/etesevimab (Bam/Ete) in COVID-19				
Reference	Study design/ participants number	primary endpoints/Clinical outcome measures	Main findings	
Gottlieb <i>et</i> <i>al.</i> [62]	Randomized phase 2/3 trial, the BLAZE-1 study, mild/moderate people Bam 7000 mg (n = 101) Bam 2800 mg (n = 107) Bam 700 mg (n = 101) Placebo (n = 156) Bam/Ete 2800 mg each (n = 112)	Alter in a load of log viral (11d) SE: 3 Measures of other viral load, measures of 5 symptoms, and measure of 1 clinical result [ED visits, hospitalization, and/or death (29d)]	$\begin{array}{l} & \text{Bam/Ete versus placebo,}\\ \text{load of log viral difference} = -0.57 (11d) (95\% \text{ CI} = (-1.00) \text{-}\\ (-0.14); \text{P} = 0.01) (\text{statistically notable}), \text{bam 700 mg was}\\ 0.09 (95\% \text{ CI} = (-0.35) \text{-}(0.52); \text{P} = 0.69),\\ \text{for bam 2800 mg was} -0.27 (95\% \text{ CI, } -0.71 \text{-} 0.16; \text{P} = 0.21),\\ \text{for bam, 7000 mg was} 0.31 (95\% \text{ CI, } -0.13 \text{-} 0.76; \text{P} = 0.16)\\ \text{(NS),}\\ \text{statistically remarkable differences between each group}\\ \text{versus placebo in 10/84 points of secondary findings,}\\ \text{hospitalization/ED visits} 0.9\% \text{ versus 5.8\%}\\ \text{a statistically notable alter from the base (29d)} \end{array}$	
Lundgren <i>et</i> <i>al.</i> [73]	Hospitalized people, double-blind trial, randomized Placebo + RDV (n = 151) Bam + RDV (n = 163)	Sustained improvement after 90 days, two sequential findings (5d)	Bam versus placebo, 50% versus 54% fell in one of the two most desirable categories of the pulmonary finding on a scale of 7-point ordinal (5d), overall falling OR in a more desirable category was 0.85 (95% CI = 0.56-1.29; P = 0.45), alike PEs (19% versus 14%; 95% CI = 0.78-3.10; OR = 1.56; P = 0.20), the ratio of sustained recovery rate was 1.06 (95% CI = 0.77-1.47)	
Chen <i>et al.</i> [63]	Mild/moderate outpatients, ongoing, phase 2 RCT, double-blind Placebo (n = 143) Bam 7000 mg (n = 101) Bam 2800 mg (n = 107) Bam 700 mg (n = 101)	Alter from a base in a load of viral (11d)	Bam 2800 mg versus placebo, the difference in a reduction from a base in a load of viral -0.53 (95% CI = (-0.98)-(-0.08); P = 0.02) and a load of viral shorter by a 3.4 factor (Only dose with a statistically remarkable reduction), slightly shorter symptom intensity (2-6d), hospitalization 1.6% versus 6.3%	
Dougan <i>et al.</i> [64]	For mild/moderate patients, phase three RCT Placebo (n = 517) Bam/ete (n = 518)	In total clinical situation (death and hospitalization)	Bam/ete versus placebo, shorter hospitalization (-4.8 percentage points, absolute risk difference; 95% CI = (-7.4)-(-2.3); relative hazard difference, 70%; P < 0.001), a remarkable decrease in a load of log viral, the difference from placebo in the alter from the base, -1.20; 95% CI = (-1.46) to (-0.94); P < 0.001)	
		Casirivimab/imdevin	nab (REGN-COV2)	
Reference	Study design/ number of participants (n)	primary endpoints/ Clinical outcome measures	Main findings	
	Ongoing, non-hospitalized patients, Phase 1–3 RCT.	Time-weighted average alter in viral	REGN-COV-2 versus placebo, least-squares mean difference in the primary endpoint was	

Table 6. Neutralizing monoclonal antibodies versus SARS-CoV-2

Weinreich <i>et</i> al. [67]	Ongoing, non-hospitalized	Time-weighted	REGN-COV-2 versus placebo,
	patients, Phase 1-3 RCT,	average alter in viral	least-squares mean difference in the primary endpoint was
	double-blind	load from baseline	-0.56 log10 copies/ml (95% CI, -1.02 to -0.11) in serum-
	Placebo $(n = 93)$	(7d)	negative people and -0.41 log10 copies/ml (95% CI, -0.71
	REGN-COV2 2.4 g (n =		to -0.10) in the overall population,
	92)	SE: alter in viral load	3% versus 6% of people stated at least 1 medical visit,
	REGN-COV2 8.0 g (n =	from baseline to	in serum antibody-negative people, 6% versus 15%
	90)	different days	(difference, -9 percentage points; 95% CI, -29-11)

CT-P59 in COVID-19					
Author/date	Study design/ number of participants (n)	primary endpoints/ Clinical outcome measures	Main findings		
Eom <i>et al.</i> [70]	Phase 2/3 double-blind RCT, mild/moderate outpatients. Placebo (n = 103) CT-p50 40 mg/kg (n = 101) CT-p50 80 mg/kg (n = 103)	Time to negative conversion, nasopharyngeal swab (28d), clinical recovery (14d)	CT-P59 40 mg/kg versus 80 mg/kg versus placebo, the median time to negative conversion, 12.8d (9.00– 12.84) versus 11.9d (8.94-12.91) versus 12.9d (12.75– 13.99), (95% CI), median time to improvement, 5.4d (3.97-6.78) versus 6.2d (5.53-7.85) versus 8.8d (6.72-11.73), lower oxygen or hospitalization (4.0% [1.6–9.7%]) versus (4.9% [2.1–10.9%]) versus (8.7% [4.7–15.8%), v ratios of corresponding improvement rate (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), ratios of clinical recovery (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

Casirivimab/imdevimab, bamlanivimab/etesevimab, and sotrovimab are monoclonal antibodies that now reduce viral loads and have FDA emergency utilization authorization for the treatment of mild to moderate COVID-19 in high-risk children and adults [74]. It is hoped that the many different neutralizing antibodies being studied will yield positive outcomes. RDV is now the only antiviral medication licensed by the FDA for severe COVID-19. The WHO SOLIDARITY trial and other recent data suggest that monotherapy is not very effective, particularly when it comes to lowering mortality. Nonetheless, there is some proof that it helps patients undergoing oxygen therapy recover faster. Currently, several promising new antiviral candidates may be efficient against SARS-CoV-2. These include favipiravir (enhanced viral clearance), nitazoxanide (lower viral loads, decreased hospitalization, and illness progression), and sofosbuvir/daclatasvir (decreased hospitalization time, decreased rates of mortality, and considerably boosted clinical recovery). These need more clinical research. Furthermore, novaferon and nafamostat-mesilate might be helpful options for treating COVID-19, although further research is needed to verify their possible effectiveness.

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(9393):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, Din IU, 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.
- 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
- Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, Cao JM. SARS-CoV-2: structure, biology, and structurebased 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
- 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
- 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):S41-6. doi:10.4103/ija.IJA_149_21
- 20. 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
- 21. 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
- 22. 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
- 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
- 24. 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
- 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

- 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
- 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
- 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(1):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. 2020:2020-03. 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(1):538-43. doi:10.1016/j.ijid.2020.11.008
- 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
- 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
- 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(19):1787-99.
- 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.
- 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 doubleblind 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. 2021:2021-04. doi:10.1101/2021.04.19.21255441
- 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. 2021:2021-03. doi:10.1101/2021.03.03.21252509
- 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
- 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=E715C3253203F90E4F6D421915B8 3EE65CE9BB2265AD5DA2D04BA7DCD4193E2EA91EEA5685452349FA826A42B0C78460&originRe gion=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):ofaa241. 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(8):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
- 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, Ajithdoss D, Copin R, Zhou A, Lanza K, Negron N, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science. 2020;370(6520):1110-5. doi:10.1126/science.abe2402
- 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
- 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
- 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
- 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
- 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
- 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)