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An update on drugs with therapeutic potential for SARS-CoV-2 (COVID-19) treatment

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ABSTRACT

The COVID-19 pandemic is one of the greatest threats to human health in the 21st century with more than 257 million cases and over 5.17 million deaths reported worldwide (as of November 23, 2021. Various agents were initially proclaimed to be effective against SARS-CoV-2, the etiological agent of COVID-19. Hydroxychloroquine, lopinavir/ritonavir, and ribavirin are all examples of therapeutic agents, whose efficacy against COVID-19 was later disproved. Meanwhile, concentrated efforts of researchers and clinicians worldwide have led to the identification of novel therapeutic options to control the disease including PAXLOVID™ (PF-07321332). Although COVID-19 cases are currently treated using a comprehensive approach of anticoagulants, oxygen, and antibiotics, the novel Pfizer agent PAXLOVID™ (PF-07321332), an investigational COVID-19 oral antiviral candidate, significantly reduced hospitalization time and death rates, based on an interim analysis of the phase 2/3 EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) randomized, double-blind study of non-hospitalized adult patients with COVID-19, who are at high risk of progressing to severe illness. The scheduled interim analysis demonstrated an 89 % reduction in risk of COVID-19-related hospitalization or death from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint). However, there still exists a great need for the development of additional treatments, as the recommended therapeutic options are insufficient in many cases. Thus far, mRNA and vector vaccines appear to be the most effective modalities to control the pandemic. In the current review, we provide an update on the progress that has been made since April 2020 in clinical trials concerning the effectiveness of therapies available to combat COVID-19. We focus on currently recommended therapeutic agents, including steroids, various monoclonal antibodies, remdesivir, baricitinib, anticoagulants and PAXLOVID™ summarizing the latest original studies and meta-analyses. Moreover, we aim to discuss other currently and previously studied agents targeting COVID-19 that either show no or only limited therapeutic activity. The results of recent studies report that hydroxychloroquine and convalescent plasma demonstrate no efficacy against SARS-CoV-2 infection. Lastly, we summarize the studies on various drugs with incoherent or insufficient data concerning their effectiveness, such as amantadine, ivermectin, or niclosamide.

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1. Introduction

Coronaviruses (CoVs) are enveloped, spherical viruses, whose genome contains a positive-sense, single-strained RNA (Cui et al., 2019; Pollard et al., 2020). They are responsible for respiratory and interstitial infections, whose severity varies from cold-like symptoms to severe respiratory failure (Fehr and Perlman, 2015; Giovanetti et al., 2021). The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes the Coronavirus Disease 2019 (COVID-19), whose symptoms can vary from mild, self-limiting respiratory distress to severe pneumonia leading to multiple organ failure and death (Huang et al., 2020). To date, the World Health Organization (WHO) has reported nearly 257 million COVID-19 cases and more than 5.17 million deaths worldwide (World Health Organization, 2021) (as of November 23, 2021).

The genome of the SARS-CoV-2 encodes multiple structural, as well as 16 non-structural proteins necessary for transcription and replication (Fehr and Perlman, 2015; Perlman and Netland, 2009), such as the membrane protein (M), spike protein (S), envelope protein (E), and nucleocapsid protein (N) (Fig. 1) (Kirtipal et al., 2020). Similar to other RNA viruses, the genome of SARS-CoV-2 is prone to random mutations that affect both structural and non-structural genes (Giovanetti et al., 2021; Aleem et al., 2021). As a result of this genetic diversity, SARS-CoV-2 variants of concern (VOC) have emerged around the world, posing a possible threat to public health. The genetic alterations change the viral phenotype and affect its transmissibility, virulence, and severity of clinical manifestation (World Health Organization, 2021; Aleem et al., 2021). Since the beginning of the pandemic, the WHO has named five variants as VOCs, namely the Alpha, Beta, Gamma, Delta, and Omicron variants, which have spread worldwide (World Health Organization, 2021). With the emergence of novel variants, the rapid evaluation of possible resistance to anti-viral therapies and vaccines is highly required. However, data on the efficacy of available therapeutic agents and vaccines against VOC is clearly insufficient. For example, the Beta and Gamma variants demonstrated decreased susceptibility *in vitro* to treatment with bamlanivimab and etesevimab, a combination of anti-SARS-CoV-2 monoclonal antibodies (mAb) (COVID-19 Treatment Guidelines Panel, 2021; Food and Drug Administration, 2021a). However, this combination shows no reduced susceptibility (<5-fold reduction) towards the Alpha, Delta and Lambda variants. The clinical implication of these findings has yet to be established. Nevertheless, sotrovimab and a combination of casirivimab and imdevimab showed sufficient activity against all VOCs (COVID-19 Treatment Guidelines Panel, 2021; Food and Drug Administration, 2020, 2021b). The emergence of highly transmissible variants, combined with the easing of travel restrictions and low vaccination rates in some countries may lead to a further rise in reported cases, hospitalization rates, and deaths (World Health Organization, 2021).

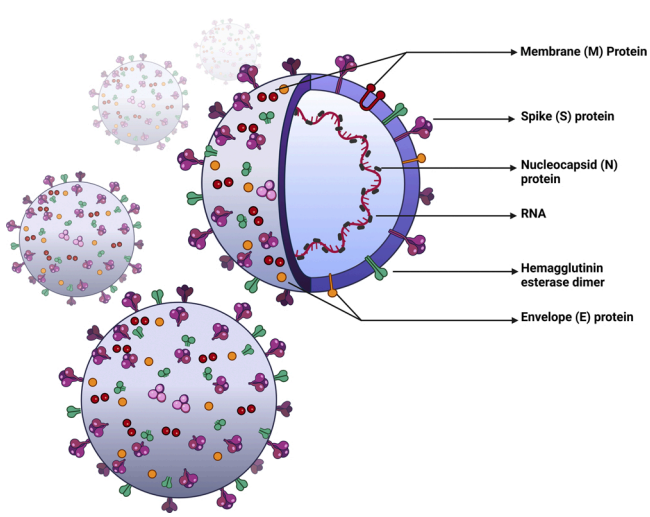

Fig. 1. Schematic depiction of SARS-Cov-2. SARS-Cov-2 is an enveloped, spherical virus belonging to the coronaviridae family. RNA – genomic, positive-sense, single-stranded RNA, M – membrane protein, S – spike protein, N – nucleocapsid protein, E – envelope protein.

Since the beginning of the pandemic, multiple antivirals, antibiotics, antimalarials, and immunomodulatory drugs were predicted to be effective against SARS-CoV-2 (Fig. 2). However, further studies reported limited or no clinical usefulness for most proposed drugs. However, identification of agents that are ineffective is of paramount importance, so that both proper and effective treatment is applied, and possible undesired side-effects of treatment are avoided. In the current review, we aim to provide an update on the advancements in clinical trials assessing the clinical efficacy of those treatment modalities that has been made since April 2020 and provide insight into future perspectives (Tables 1 and 2). The current recommendations for COVID-19 treatment are summarized in Table 3.

2. Vaccines

The introduction of COVID-19 vaccines in late 2020 has provided an opportunity to restrict the transmission of the SARS-CoV-2 virus and reduce the number of hospitalizations and deaths (Fig. 3). The US Food and Drugs Administration (FDA) has approved the Pfizer-BioNTech COVID-19 vaccine, Moderna COVID-19 Vaccine, and Janssen COVID-19 Vaccine for emergency use in the USA, while the European Medicines Agency (EMA) also authorized the vaccine developed by AstraZeneca. Furthermore, other vaccines are being used around the world and many more are still being developed. The efficacy and safety of the most frequently used vaccines are summarized in Table 4. According to the WHO, almost 7.7 billion doses of vaccines have been administered and approximately 53.2 % of the world's population have received at least the first vaccine dose. However, most vaccines were distributed in a small number of highly developed countries, leaving most of the developing world susceptible to SARS-CoV-2 infection. Furthermore, the data evaluating the efficacy of vaccines against VOC is limited and inconsistent, yet full vaccination appears to protect against a severe course of illness and death from all occurring VOCs (World Health Organization, 2021; Fontanet et al., 2021; Lopez Bernal et al., 2021). Moreover, multiple studies have shown waning immunity acquired after vaccination, especially in immunocompromised patients, for example those undergoing hemodialysis or cytotoxic cancer drug treatment. This contributes to an increasing number of breakthrough infections (Shroff et al., 2021; Juno and Wheatley, 2021; Goldberg et al., 2021; Fowlkes et al., 2021; Davidovic et al., 2021; Campo et al., 2021). Currently, several countries have developed various strategies to tackle this problem, among which, additional doses of COVID-19 vaccines have shown to be safe and efficient in boosting immune response (Yue et al., 2021; Falsey et al., 2021; Dekervel et al., 2021; Choi et al., 2021; Barros-Martins et al., 2021). Nonetheless, the low vaccination rate, coupled with the risk of emergence of vaccine-resistant SARS-CoV-2 variants and waning immunity, emphasizes the burning need to develop novel drugs and therapeutic modalities for COVID-19 (Artese et al., 2020; Twomey et al., 2020; Drożdżal et al., 2020).

3. Recommended therapeutic agents/potential treatment

3.1. Monoclonal antibodies

Bamlanivimab (LY-CoV555) is a potent neutralizing IgG1 mAb against the SARS-CoV-2 spike protein. It is designed to block viral attachment and entry into human cells, thus neutralizing the virus and potentially preventing and treating COVID-19 (Anon, 2006; Jones et al., 2021).

Etesevimab (also known as JS016 or LY-CoV016) is a fully

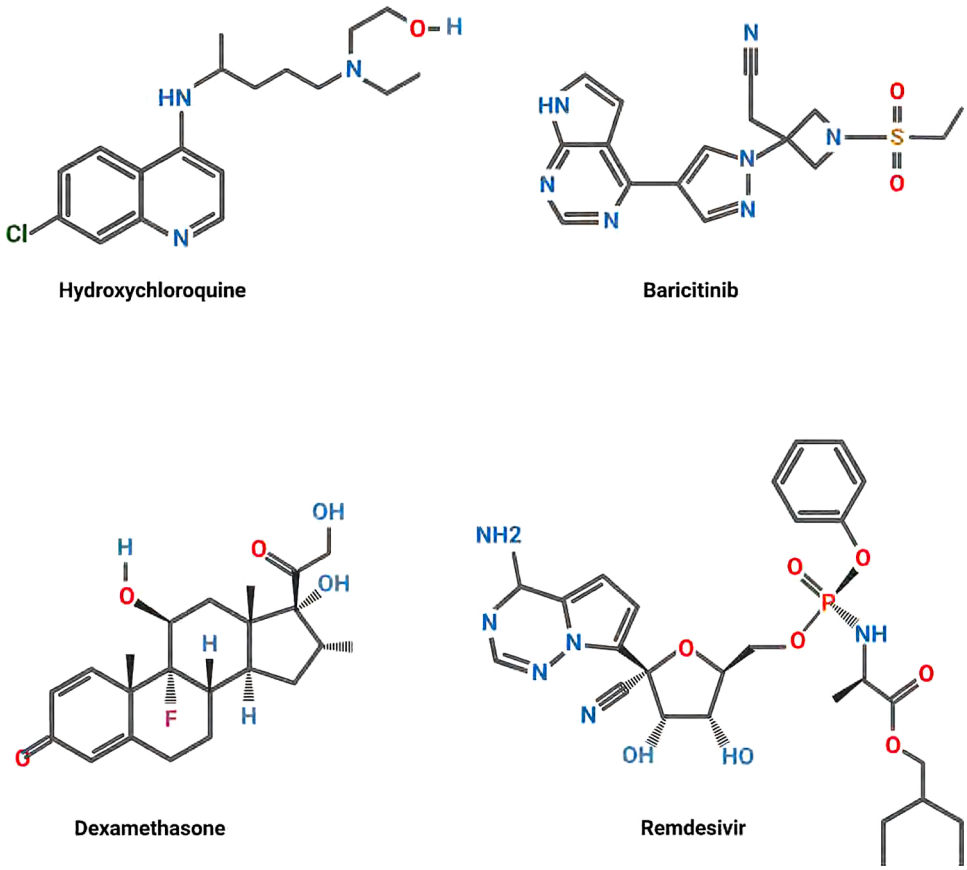

Fig. 2. Examples of drugs proposed for the treatment of SARS-CoV-2. Structural renderings of Hydroxychloroquine (antimalarial drug, potential blocker of viral maturation), Baricitinib (anti-inflammatory: blocker of JAK-1, JAK-2 kinases), Dexamethasone (steroid anti-inflammatory drug), and Remdesivir (blocks viral replication) are shown.

humanized recombinant neutralizing mAb that specifically binds to the SARS-CoV-2 surface protein receptor-binding domain (RBD) with high affinity and can effectively block virus binding to the host angiotensin converting enzyme 2 (ACE-2) receptor on the cell surface (Anon, 2006).

In a phase 3 study, Dougan et al., randomized a 1:1 cohort of outpatients with mild to moderate COVID-19, who were at high risk of progressing to severe disease, have received a single intravenous infusion of mAbs. This therapy was administered to patients at doses of 2800 mg (bamlanivimab) and 2800 mg (etesevimab) or a placebo within 3 days following laboratory diagnosis of SARS-CoV-2 infection. The primary endpoint was the overall clinical status of the patients, defined as hospitalization for COVID-19 or all-cause death by day 29. A total of 1035 patients participated in the study, with a mean age (± SD) of 53.8 ± 16.8 years. By day 29, a total of 11 out of 518 patients (2.1 %) in the bamlanivimab-etesevimab group were hospitalized or died from COVID-19, compared with 36 of 517 patients (7.0 %) in the placebo group [absolute risk difference = -4.8 percentage points (95 % CI: -7.4 – -2.3); relative risk difference = 70 %; $p < 0.001$]. There were no deaths in the bamlanivimab-etesevimab group, although there were 10 deaths in the placebo group, 9 of which were assessed by the investigators as related to COVID-19. At Day 7, there was a greater log reduction from baseline in viral load for patients who received bamlanivimab with etesevimab than for patients who received a placebo ($p < 0.001$). The authors of the study have concluded that in high-risk outpatients, the use of mAbs led to fewer hospitalizations and deaths associated with COVID-19 than with a placebo. Moreover, such therapy accelerated the decline in SARS-CoV-2 viral load (Dougan et al., 2021).

Gottlieb et al., in their randomized phase 2/3 BLAZE-1 trial, evaluated the effect of bamlanivimab monotherapy and combined therapy with etesevimab on SARS-CoV-2 virus load in mild to moderate COVID-19. The first group of patients received a single infusion of bamlanivimab, the second received both mAbs, and the third group received placebo. Compared to the placebo, the difference in log viral load-change at day 11 was statistically significant [-0, 57 (95 % CI: -1.00 – -0.14; $p = 0.01$)] only for combined therapy, and there were no deaths recorded during study treatment. The authors of the study concluded that in non-hospitalized patients with mild to moderate COVID-19 disease, treatment with bamlanivimab and etesevimab compared to a placebo was associated with a statistically significant reduction in SARS-CoV-2 viral load on day 11 (Gottlieb et al., 2021).

Sotrovimab (Xevudy, GlaxoSmithKline and Vir Biotechnology, Inc.) is a recombinant engineered human IgG1 mAb that binds to a highly conserved epitope on the S protein RBD of SARS-CoV-2 with high affinity, but it does not compete with human ACE-2 receptor binding (Anon, 2021). The efficacy of sotrovimab was evaluated in an interim analysis of the ongoing COMET-ICE study. Patients were treated with a single 500 mg infusion of sotrovimab (N = 291) or a placebo (N = 292) over 1 h. The median age of the overall randomized population was 53 years (range: 18–96). The clinical progression of COVID-19 at Day 29 in recipients of sotrovimab was reduced by 85 % compared with the placebo group ($p = 0.002$) (Anon, 2021).

Casirivimab (IgG1-κ) and **imdevimab** (IgG1-λ) are recombinant human mAbs, which are unmodified in the Fc regions. The mAbs bind to non-overlapping epitopes of the spike protein RBD of SARS-CoV-2, and thereby block binding to the human ACE-2 receptor (Anon, 2020). An ongoing phase 1–3 trial in non-hospitalized COVID-19 patients investigated the effect of the mix of these antibodies (REGN−COV2) to reduce the risk of developing a refractory mutant virus. Patients were randomly assigned (1:1:1) to receive a placebo, 2.4 g of REGN−COV2, or 8.0 g of REGN−COV2 and were prospectively characterized at baseline for the

Table 1
Summary of currently conducted studies on COVID-19 drugs according to: drugvirus.info (Andersen et al., 2020; Drugvirus.info, 2021), clinicaltrials.gov (US National Library of Medicine, 2020) (updated on – 27th of July 2021).

Therapeutic agent	Number of phase III-IV clinical trials
Amantadine	3
ASA	10
Azithromycin	41
Bamlanivimab - etesevimab	3
Baricitinib	13
Camostat mesylate	6
Casirivimab/ imdevimab	3
Chloroquine	13
Dexamethasone	29
Favipiravir	21
HCQ	117
Imatinib	2
IFN-β-1a	11
Isotretinoin	3
Ivermectin	37
Lopinavir/ritonavir	20
Mefloquine	2
Nafamostat mesylate	5
Niclosamide	4
Nitazoxanide	18
Oseltamivir	7
Remdesivir	46
Ribavirin	3
Sofosbuvir	8
Sotrovimab	2
Tocilizumab	23
Umifenovir	4

Legend: ASA – acetylsalicylic acid, aspirin; HCQ – hydroxychloroquine; IFN-interferon.

endogenous immune response against SARS−COV-2 (serum antibody-positive or serum antibody-negative). Key endpoints included the time-weighted average change in viral load from baseline (day 1) through day 7 and the percentage of patients with at least one COVID-19-related co-morbidity who attended a clinic visit through day 29. Data from 275 patients are reported; the least-squares mean difference (the combined REGN−COV2 dose groups vs. the placebo group) in the time-weighted average change in viral load from day 1 through day 7 was -0.56 $\log_{10}$ copies per milliliter (95 % CI: -1.02 – -0.11) among patients who were serum antibody-negative at baseline and -0.41 $\log_{10}$ copies per milliliter (95 % CI: -0.71 – -0.10) in the overall trial population. In this interim analysis, REGN−COV2 reduced viral load, and to a greater extent in patients whose immune response had not yet been initiated or who had a high viral load at baseline (Weinreich et al., 2021).

Tocilizumab (RoActemra, Roche Pharma AG) is a recombinant humanized IgG1 mAb that binds specifically to both soluble and membrane-bound receptors for IL-6 (sIL-6R and mIL-6R), thereby inhibiting this signaling pathway, and reducing the pro-inflammatory effect of IL-6 (Sebba, 2008). In their dissertation, Malgie et al., reviewed and performed a meta-analysis of observational studies evaluating the effect of tocilizumab on COVID-19 patient mortality. The authors included 10 studies related to the use of tocilizumab, totaling 1358 patients, with nine out of ten studies found to be of high quality. The meta-analysis showed that the mortality in the tocilizumab group was lower than in the control group [RR = 0.27 (95 % CI: 0.12 – 0.59); the risk difference = 12 % (95 % CI: 4.6%–20%)]. With only a few studies available, no difference in side effects has been observed. Mortality was 12 % lower in the group of patients who received tocilizumab compared to those who did not, although these results require confirmation in randomized controlled trials (RCTs) (Malgie et al., 2021).

In another review by Arthur et al., researchers analyzed 10 RCTs evaluating the effect of tocilizumab in COVID-19 in which they allocated patients to two groups. The control group received the standard care, while the treatment group was comprised of patients who received tocilizumab in addition to standard care; the primary outcome was 28 to 30-day mortality. Secondary endpoints included progression to severe disease, defined as the need for mechanical ventilation, intensive care unit (ICU) admission, or complex disease. Out of 6493 patients, 3358 (52.2 %) were allocated to tocilizumab. The results demonstrated that tocilizumab use was associated with decreased mortality [24.4 % vs. 29.0 %; odds ratio (OR) = 0.87 (95 % CI: 0.74–1.01); p = 0.07]. Tocilizumab did reduce the need for mechanical ventilation and was associated with an advantage in the composite secondary endpoint, but did not reduce the number of ICU admissions (Arthur et al., 2021).

However, the results of a phase 3 trial were contradictory. The NCT04320615 study described by Rosas et al., did not present a difference between tocilizumab and placebo groups [mortality at day 28 was 19.7 % – the tocilizumab group and 19.4 % – the placebo group (95 % CI = -7.6–8.2; p = 0.94)] (Rosas et al., 2021). A Study authors suggests considering the use of tocilizumab in hospitalized COVID-19 patients with hypoxia and laboratory signs of significant inflammation.

3.2. Remdesivir

Remdesivir is an adenosine analogue that is metabolized to its active metabolite, remdesivir triphosphate. Remdesivir triphosphate is a structural analogue of adenosine triphosphate (ATP) and competes with the natural substrate for the incorporation by RNA polymerase into nascent viral RNA, which results in delayed chain termination during replication and consequently inhibition of viral replication (Fig. 4) (Singh et al., 2020).

One of the most recent and largest studies that describes the effectiveness of remdesivir in SARS-CoV-2 infection reports that despite its conditional recommendation, remdesivir may still be effective in achieving early clinical improvement. It reduces early-stage mortality and the need for high flow oxygen supplementation and invasive mechanical ventilation among hospitalized COVID-19 patients. Treatment with remdesivir was associated with an increase in clinical recovery rate by 21 % [risk ratio (RR) = 1.21 (95 % CI: 1.08–1.35)] on day 7 and 29 % [RR = 1.29 (95 % CI: 1.22–1.37)] on day 14. The likelihoods of requiring high-flow supplemental oxygen and invasive mechanical ventilation in the remdesivir group were lower than in the placebo group by 27 % [RR = 0.73 (95 % CI: 0.54 – 0.99)] and 47 % [RR = 0.53 (95 % CI: 0.39 – 0.72)], respectively. Remdesivir-treated patients showed a 39 % [(RR = 0.61 (95 % CI: 0.46 – 0.79)] reduction in the risk of mortality on day 14 compared to the control group; however, there was no significant difference on day 28 (Angamo et al., 2021). A Study authors suggests considering the use of remdesivir in patients with confirmed SARS-CoV-2 infection during the period of viral replication (i.e., not later than 5–7 days from the onset of the first symptoms of the disease) in patients with documented pneumonia and peripheral blood oxygen saturation (SpO2) ≤ 94 % (when breathing atmospheric air).

3.3. Baricitinib

Baricitinib is a selective inhibitor of janus activated kinase 1 (JAK1) and janus activated kinase 2 (JAK2), the two of which mediate signaling for cytokines and growth factors involved in hematopoiesis, inflammation, and the immune response. It modulates intracellular signaling by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing phosphorylation and activation of STAT proteins. Baricitinib inhibits the induction of IL-6 in a dose dependent manner while also reducing the serum concentration of C-reactive protein (CRP) (Stebbing et al., 2020).

In a multi-center study, the beneficial impact of baricitinib was tested in COVID-19 patients with moderate pneumonia (Cantini et al., 2020). At baseline, 113 patients were included in the baricitinib-arm, and 78 in the control-arm. The results indicate that the 2-week case fatality rate was significantly lower in the baricitinib-arm compared with controls [0% (0/113) vs. 6.4 % (5/78) (p = 0.010; 95 % CI: 0.0000 – 0.4569)]. ICU admission was necessary in 0.88 % (1/113) patients in

Table 2
An update on the clinical trials on COVID (as of the 29th of July 2021) (US National Library of Medicine, 2020).

Therapeutic agent	Clinical trial ID	Number of participants	status	Additional information
Abidol	NCT04255017	400	recruiting	compared to oseltamivir, lopinavir/ritonavir, standard of care
Adalimumab	NCT04705844	1444	not yet recruiting	compared to placebo
Adalimumab	ChiCTR2000030089	60	active, not recruiting	compared to standard treatment
Adamumab + Tozumab	ChiCTR2000030580	60	recruiting	compared to standard treatment
Amantadine	NCT04952519	500	recruiting	compared to placebo
Amantadine	NCT04894617	226	not yet recruiting	compared to placebo
Amantadine	NCT04854759	200	recruiting	compared to placebo
Amiodarone	NCT04351763	804	recruiting	compared to verapamil, standard of care
Anakinra	NCT04680949	606	active	compared to placebo
Anakinra	NCT04424056	216	not yet recruiting	combined with ruxolitinib; compared to tocilizumab, tocilizumab + ruxolitinib, standard of care
Anakinra	NCT04362111	30	recruiting	compared to placebo
Anakinra	NCT04443881	179	completed	compared to standard of care
Anakinra	NCT04643678	80	recruiting	compared to standard of care
Anakinra	NCT04341584	240	completed	–
Anakinra	NCT04339712	20	completed	compared to tocilizumab
Anakinra	NCT04324021	54	terminated	compared to emapalumab and standard treatment
Angiotensin 1−7	NCT04332666	60	not yet recruiting	–
ACE-I	NCT04345406	60	not yet recruiting	compared to standard of care
ACE-Is & ARBs	NCT04353596	216	completed	stopping of ACEI/ARB treatment compared to further ACEI/ARB treatment
ACE-Is & ARBs	NCT04591210	1155	recruiting	compared to no treatment
ACE-Is & ARBs	NCT04493359	240	recruiting	compared to standard of care
ARBs	NCT04394117	1500	recruiting	compared to placebo
Anti-SARS-CoV-2 equine hyperimmune serum	NCT04838821	156	active	compared to placebo
Apremilast	NCT04590586	516	active	compared to landelumab, zilucoplan, placebo
Arbidol	NCT04260594	304	completed, has results	compared to standard of care
ASC09	NCT04261270	60	recruiting	combined with oseltamivir; compared to ritonavir + oseltamivir, oseltamivir
ASC09	NCT04261270	60	recruiting	compared to ritonavir; combined with oseltamivir
ASC09	NCT04261907	160	not yet recruiting	compared to lopinavir/ritonavir; combined with ritonavir
ASA	NCT04365309	128	recruiting	compared to standard of care
Atazanavir	NCT04468087	1005	recruiting	compared to daclatasvir, sofosbuvir + daclatasvir, placebo
Atovaquone	NCT04339426	25	recruiting	combined with azithromycin
Aviptadil	NCT04311697	196	completed	compared to placebo
AZD7442	NCT04723394	1700	recruiting	compared to placebo
Azithromycin	NCT04359316	40	not yet recruiting	combined with HCQ
Azithromycin	NCT04381962	298	completed	compared to standard of care
Azithromycin	NCT04363060	104	not yet recruiting	combined with amoxicillin/clavulanate; compared to amoxycillin/clavulanate
Azithromycin	NCT04341727	500	suspended	compared to chloroquine and hydroxychloroquine
Azithromycin	NCT04324463	1500	recruiting	compared to chloroquine
Azithromycin	NCT04339816	240	terminated	combined with hydroxychloroquine
Azithromycin	NCT04336332	160	active, not recruiting	compared to hydroxychloroquine; combined with hydroxychloroquine
Azithromycin	NCT04332107	2271	active, not recruiting	–
Azithromycin + Hydroxychloroquine	NCT04322123	630	active, not recruiting	compared to HCQ
Azithromycin + Hydroxychloroquine	NCT04321278	440	completed	compared to HCQ
Azoximer Bromide	NCT04381377	394	active	compared to placebo
Azvudine	NCT04668235	342	recruiting	compared to placebo
Azvudine	ChiCTR2000029853	20	recruiting	compared to standard treatment
Azvudine	ChiCTR2000030041	40	not yet recruiting	–
Azvudine	ChiCTR2000030424	30	not yet recruiting	–
Azvudine	ChiCTR2000030487	10	recruiting	–
Bactek-R	NCT04363814	100	recruiting	compared to standard of care
Baloxavir marboxil	ChiCTR2000029544	30	not yet recruiting	compared to favipiravir and standard treatment
Baloxavir marboxil	ChiCTR2000029548	30	not yet recruiting	compared to favipiravir and lopinavir/ritonavir
Bamlanivimab	NCT04656691	4000	completed	single group assignment
Bamlanivimab	NCT04796402	576	recruiting	compared to standard of care
Bamlanivimab	NCT04748588	648	recruiting	compared to standard of care
Bamlanivimab	NCT04518410	2000	recruiting	compared to BRII-196/BRII-198, AZD7442, SGN001, Camostat, C135-LS + C144-LS, SAB-185, placebo
Baricitinib	NCT04401579	1033	completed	combined with remdesivir; compared to remdesivir + placebo
Baricitinib	NCT04640168	1010	active	combined with remdesivir; compared to dexamethasone and remdesivir
Baricitinib	NCT04970719	382	recruiting	combined with remdesivir; compared to dexamethasone plus remdesivir
Baricitinib	NCT04421027	1585	completed	compared to placebo

(*continued on next page*)

Table 2 (*continued*)

Therapeutic agent	Clinical trial ID	Number of participants	status	Additional information
Baricitinib	NCT04358614	12	completed	crossover assignment
Baricitinib	NCT04320277	60	not yet recruiting	–
Baricitinib	NCT04340232	80	withdrawn	–
Baricitinib	NCT04321993	1000	recruiting	compared to HCQ, lopinavir/ritonavir and sarilumab
BDB-001	NCT04449588	368	recruiting	compared to standard of care
BLD-2660	NCT04334460	120	active, not recruiting	–
BNO 1030	NCT04797936	133	completed	compared to standard of care
Brazilian Green Propolis Extract	NCT04480593	120	completed	compared to placebo
Brensocatib	NCT04817332	400	completed	compared to placebo
Bromhexidine	NCT04355026	90	recruiting	combined with HCQ; compared to HCQ
Bucillamine	NCT04504734	1000	recruiting	compared to placebo
Budesonid	NCT04361474	120	completed	compared to placebo
Budesonid	NCT04355637	300	recruiting	compared to standard of care
C21	NCT04880642	600	not yet recruiting	compared to placebo
Camostat Mesylate	NCT04608266	596	recruiting	compared to placebo
Camostat Mesylate	NCT04657497	155	completed	compared to placebo
Camostat Mesylate	NCT04321096	180	recruiting	–
Canakinumab	NCT04362813	451	completed	compared to placebo
Canakinumab	NCT04510493	116	recruiting	compared to placebo
Cannabidiol	NCT04467918	100	active	compared to placebo
Cannabidiol	NCT04615949	422	recruiting	compared to placebo
Carrimycin	NCT04672564	300	recruiting	compared to placebo
CD24Fc	NCT04317040	243	completed	compared to placebo
CD24Fc	NCT04317040	230	completed	–
Cefditoren pivoxil	NCT04709172	30	recruiting	single group assignment
Cetirizine + Famotidine	NCT04836806	160	recruiting	compared to placebo
Chloroquine	ChiCTR2000029542	20	recruiting	compared to standard treatment
Chloroquine	ChiCTR2000029609	200	not yet recruiting	compared to lopinavir/ritonavir
Chloroquine	ChiCTR2000029741	112	recruiting	compared to lopinavir/ritonavir
Chloroquine	ChiCTR2000029826	45	not yet recruiting	–
Chloroquine	ChiCTR2000029837	120	not yet recruiting	–
Chloroquine	ChiCTR2000029935	100	recruiting	–
Chloroquine	ChiCTR2000029939	100	recruiting	compared to standard treatment
Chloroquine	ChiCTR2000029975	10	not yet recruiting	–
Chloroquine	ChiCTR2000029988	80	recruiting	compared to standard treatment
Chloroquine	ChiCTR2000029992	100	not yet recruiting	compared to standard treatment; combined with HCQ
Chloroquine	ChiCTR2000030031	120	suspended	–
Chloroquine	ChiCTR2000030417	30	suspended	–
Chloroquine	ChiCTR2000030718	80	recruiting	compared to standard treatment
Chloroquine	ChiCTR2000029898	100	recruiting	compared to hydroxychloroquine
Chloroquine	ChiCTR2000029899	100	recruiting	compared to HCQ
Chloroquine	NCT04341727	500	suspended	compared to azithromycin and CQ
Chloroquine	NCT04324463	1500	recruiting	compared to azithromycin
Chloroquine	NCT04323527	440	completed	–
Chloroquine	NCT04333628	210	terminated	compared to standard treatment
Chloroquine	NCT04331600	400	completed	–
Chloroquine	NCT04328493	250	completed	compared to standard treatment
Chlorpromazine	NCT04366739	40	not yet recruiting	compared to standard of care
Ciclesonide	NCT04377711	400	completed	compared to placebo
Ciclesonide	NCT04330586	141	completed	compared to standard treatment; combined with HCQ
CimertrA	NCT04802382	252	recruiting	compared to placebo
Colchicine	NCT04667780	102	completed	compared to standard of care
Colchicine	NCT04350320	102	completed	compared to standard of care
Colchicine	NCT04818489	250	recruiting	compared to standard of care
Colchicine	NCT04472611	466	recruiting	combined with rosuvastatin; compared to standard of care
Colchicine	NCT04328480	1279	completed	compared to standard of care
Colchicine	NCT04492358	144	recruiting	combined with prednisone; compared to standard of care
Colchicine	NCT04416334	954	recruiting	compared to standard of care
Colchicine	NCT04328480	2500	completed	–
Colchicine	NCT04322682	6000	completed	–
Colchicine	NCT04322565	100	recruiting	–
Comega-3 Oil	NCT04836052	372	recruiting	compared to standard of care
Convalescent Plasma Therapy	NCT04425915	400	completed	compared to standard of care
Convalescent Plasma Therapy	NCT04355767	511	completed	compared to placebo
Convalescent Plasma Therapy	NCT04547660	160	completed	compared to standard of care
Convalescent Plasma Therapy	NCT04589949	690	recruiting	compared to Fresh Frozen Plasma
Convalescent Plasma Therapy	NCT04535063	200	recruiting	single group assignment
Convalescent Plasma Therapy	NCT04381858	196	completed	compared to human immunoglobulin
Convalescent Plasma Therapy	NCT04361253	220	recruiting	compared to standard plasma
Convalescent Plasma Therapy	NCT04539275	702	active	compared to placebo
Convalescent Plasma Therapy	NCT04516811	600	recruiting	compared to standard of care
Convalescent Plasma Therapy	NCT04836260	100	recruiting	single group assignment
Convalescent Plasma Therapy	NCT04567173	136	recruiting	compared to standard of care
Convalescent Plasma Therapy	NCT04345289	1100	recruiting	compared to infusion placebo
Convalescent Plasma Therapy	NCT04747158	350	completed	single group assignment

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Table 2 (*continued*)

Therapeutic agent	Clinical trial ID	Number of participants	status	Additional information
Convalescent Plasma Therapy	NCT04385043	400	recruiting	compared to standard of care
Convalescent Plasma Therapy	NCT04388410	410	recruiting	compared to placebo
Convalescent Plasma Therapy	NCT04873414	364	recruiting	compared to standard of care
Convalescent Plasma Therapy	NCT04342182	426	active	compared to standard of care
Convalescent Plasma Therapy	NCT04502472	200	recruiting	single group assignment
Convalescent Plasma Therapy	NCT04374526	29	completed	compared to standard of care
Convalescent Plasma Therapy	NCT04380935	60	recruiting	compared to standard of care
Convalescent Plasma Therapy	NCT04384588	100	recruiting	parallel assignment - cancer patients and non-cancer patients
Convalescent Plasma Therapy	NCT04816942	102	completed	single group assignment
Convalescent Plasma Therapy	NCT04332835	92	completed	compared to standard of care
Convalescent Plasma Therapy	NCT04376034	240	recruiting	compared to standard of care
Cretan IAMA	NCT04705753	20	completed	single group assignment
CSA0001	ChiCTR2000030939	10	recruiting	–
CT-P59	NCT04602000	1020	recruiting	compared to placebo
Cyclosporine	NCT04392531	120	recruiting	compared to standard of care
Dalargin	NCT04346693	320	completed	compared to standard of care
Danoprevir	NCT04345276	10	completed	combined with ritonavir
Danoprevir/Ritonavir	ChiCTR2000030000	50	recruiting	compared to IFN-α, peginterferon α-2a and standard treatment
Danoprevir/Ritonavir	ChiCTR2000030259	60	recruiting	compared to standard treatment
Danoprevir/Ritonavir	ChiCTR2000030472	20	recruiting	compared to standard treatment
Dapagliflozin	NCT04350593	1250	active	compared to placebo
Dapsone	NCT04935476	3000	not yet recruiting	compared to placebo
Darunavir/Cobicistat	NCT04252274	30	recruiting	compared to standard treatment
Darunavir/Cobicistat	NCT04304053	3040	completed	–
Darunavir/Ritonavir	NCT04291729	50	completed	compared to IFN-α, lopinavir/ritonavir and peginterferon α-2a; combined with IFN-α
DAS181	NCT04324489	4	completed	–
Deferoxamine	NCT04333550	50	recruiting	compared to standard treatment
Defibrotide	NCT04335201	50	recruiting	–
Desferal	NCT04389801	200	not yet recruiting	compared to placebo
Dexamethasone	NCT04726098	198	recruiting	high dose compared to low dose
Dexamethasone	NCT04663555	300	recruiting	high dose compared to low dose
Dexamethasone	NCT04509973	1000	active	high dose compared to low dose
Dexamethasone	NCT04509973	1000	active	high dose compared to low dose
Dexamethasone	NCT04499313	60	recruiting	compared to methylprednisolone
Dexamethasone	NCT04347980	122	recruiting	combined with HCQ; compared to HCQ
Dexamethasone	NCT04834375	142	recruiting	weight-based dexamethasone use compared to standard dexamethasone dose
Dexamethasone	NCT04765371	220	recruiting	compared to prednisolone
Dexamethasone	NCT04780581	290	recruiting	compared to methylprednisolone
Dexamethasone	NCT04327401	290	terminated	–
Dihydroartemisinin/ Piperaquine	ChiCTR2000030082	40	suspended	compared to IFN-α + umifenovir; combined with antiviral treatment
Dipyridamole	NCT04410328	132	recruiting	combined with ASA; compared to standard of care
Dornase alfa	NCT04355364	100	recruiting	compared to standard of care
Dornase alfa	NCT04402970	30	completed	compared to standard of care
Doxycycline	NCT04715295	200	recruiting	combined with rivaroxaban; compared to standard of care
Doxycycline	NCT04584567	1100	recruiting	monotherapy or combined with Zinc; compared to placebo
Doxycycline	NCT04371952	330	not yet recruiting	compared to placebo
Dutasteride	NCT04729491	138	completed	combined with azithromycin + nitazoxanide; compared to azithromycin + nitazoxanide + placebo
DWJ1248	NCT04713176	1022	recruiting	combined with remdesivir; compared to placebo
Ebastine	ChiCTR2000030535	100	recruiting	combined with IFN-α and lopinavir
EDP1815	NCT04393246	1407	recruiting	compared to dapagliflozin + ambrisentan, standard of care
Emapalumab	NCT04324021	54	terminated	compared to anakinra and standard treatment
Emtricitabine/Tenofovir	NCT04890626	2193	recruiting	compared to baricitinib + dexamethasone, dexamethasone, standard of care
Emtricitabine/Tenofovir	NCT04359095	1200	recruiting	compared to colchicine + rosuvastatin, emtricitabine/ tenofovir + colchicine + rosuvastatin, standard of care
Emtricitabine/Tenofovir + Lopinavir/Ritonavir	ChiCTR2000029468	120	not yet recruiting	–
Enisamium Iodide	NCT04682873	700	recruiting	compared to placebo
Ensovibep	NCT04828161	2100	recruiting	compared to placebo
Evolocumab	NCT04941105	60	recruiting	compared to placebo
Famotidine	NCT04370262	233	completed	compared to placebo
Favipiravir	NCT04529499	780	active	compared to placebo
Favipiravir	NCT04542694	200	completed	compared to standard of care
Favipiravir	NCT04359615	40	not yet recruiting	combined with HCQ; compared to HCQ
Favipiravir	NCT04558463	100	recruiting	compared to oseltamivir
Favipiravir	NCT04501783	168	active	compared to standard of care
Favipiravir	NCT04600895	826	recruiting	compared to placebo
Favipiravir	NCT04818320	500	active	compared to standard of care
Favipiravir	NCT04694612	676	recruiting	compared to remdesivir, placebo

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Table 2 (*continued*)

Therapeutic agent	Clinical trial ID	Number of participants	status	Additional information
Favipiravir	NCT04425460	256	not yet recruiting	compared to placebo
Favipiravir	NCT04411433	1008	active	monotherapy or combined with HCQ or azithromycin; compared to HCQ, HCQ + azithromycin
Favipiravir	NCT04600999	150	recruiting	compared to standard of care
Favipiravir	NCT04434248	330	active	compared to standard of care
Favipiravir	NCT04464408	576	recruiting	compared to placebo
Favipiravir	NCT04351295	90	recruiting	compared to placebo
Favipiravir	NCT04402203	50	recruiting	compared to standard of care
Favipiravir	NCT04373733	502	active	compared to standard of care
Favipiravir	NCT04319900	150	recruiting	monotherapy or combined with favipiravir; compared to placebo
Favipiravir	ChiCTR2000029544	30	not yet recruiting	compared to baloxavir marboxil and standard treatment
Favipiravir	ChiCTR2000029548	30	not yet recruiting	compared to baloxavir marboxil and lopinavir/ritonavir
Favipiravir	ChiCTR2000029600	90	recruiting	compared to lopinavir/ritonavir; combined with IFN-α
Favipiravir	ChiCTR2000029996	60	recruiting	–
Favipiravir	ChiCTR2000030113	20	recruiting	compared to ritonavir
Favipiravir	ChiCTR2000030254	240	completed	compared to umifenovir
Favipiravir	ChiCTR2000030987	150	recruiting	combined with chloroquine
Favipiravir	JPRN jRCTs041190120	86	completed	–
Favipiravir	NCT04273763	60	active, not recruiting	combined with bromohexine, IFN α-2b and umifenovir
Favipiravir	NCT04310228	150	recruiting	compared to tocilizumab; combined with tocilizumab
Favipiravir	NCT04336904	100	active, not recruiting	–
Fenofibrate	NCT04661930	50	recruiting	compared to placebo
Fingolimod	NCT04280588	30	withdrawn	compared to standard treatment
Fluoxetine	NCT04377308	2000	recruiting	compared to standard of care
Fluvoxamine (Lenze et al., 2020)	NCT04342663	152	completed, has results	–
Fluvoxamine	NCT04727424	3645	recruiting	compared to doxazosin, ivermectin, peginterferon λ-1a, peginterferon β-1A, placebo
Fluvoxamine	NCT04668950	1100	active	compared to placebo
Fostamatinib	NCT04629703	308	recruiting	compared to placebo
FP-025	NCT04750278	403	recruiting	compared to placebo
Furosemide	NCT04588792	640	recruiting	compared to placebo
Hydrocortisone	NCT04348305	1000	active	compared to placebo
HCQ	NCT04359953	1600	recruiting	compared to azithromycin, telmisartan, standard of care
HCQ	NCT04466540	1300	recruiting	compared to placebo
HCQ	NCT04358081	20	completed	monotherapy or combined with azithromycin; compared to placebo
HCQ	NCT04344444	600	active	monotherapy or combined with azithromycin; compared to placebo
HCQ	NCT04429867	700	active	compared to placebo
HCQ	NCT04370782	18	completed	combined with Zinc + either azithromycin or doxycycline
HCQ	NCT04405921	200	not yet recruiting	combined with azithromycin; compared to HCQ
HCQ	NCT04355052	250	recruiting	combined with azithromycin or camostat mesylate; compared to no treatment
HCQ	NCT04491994	540	completed	compared to standard of care
HCQ	NCT04420247	142	completed	compared to standard of care
HCQ	NCT04354428	300	active	monotherapy or combined with folic acid or azithromycin; compared to lopinavir / ritonavir, placebo
HCQ	NCT04351724	500	recruiting	compared to lopinavir / ritonavir, remdesivir, asunercept, standard of care
HCQ	NCT04964583	105	recruiting	combined with azithromycin; compared to HCQ, placebo
HCQ	NCT04573153	400	recruiting	combined with cofactor supplementation; compared to HCQ + sorbitol
HCQ	NCT04353336	194	completed	compared to standard of care
HCQ	NCT04652648	54	completed	compared to control
HCQ	NCT04322123	630	active	monotherapy or combined with azithromycin; compared to control
HCQ	NCT04788355	176	completed	monotherapy or combined with apixaban; compared to apixaban or placebo
HCQ	2020−000890-25 (EU-CTR)	25	ongoing	–
HCQ	ChiCTR2000029559	300	recruiting	–
HCQ	ChiCTR2000029740	78	recruiting	compared to standard treatment
HCQ (Tang et al., 2020)	ChiCTR2000029868	200	completed, has results	–
HCQ	ChiCTR2000029898	100	recruiting	compared to chloroquine
HCQ	ChiCTR2000029899	100	recruiting	compared to chloroquine
HCQ	ChiCTR2000030054	100	not yet recruting	compared to standard treatment
HCQ	NCT04261517	30	completed	compared to standard treatment
HCQ	NCT04315896	500	active, not recruiting	–
HCQ	NCT04315948	3100	active, not recruiting	compared to IFNβ-1a, lopinavir/ritonavir and remdesivir
HCQ	NCT04316377	202	active, not recruiting	compared to standard treatment
HCQ	NCT04342221	220	terminated	–
HCQ	NCT04340544	2700	terminated	–
HCQ	NCT04338698	500	recruiting	compared to azithromycin and oseltamivir
HCQ	NCT04335552	500		

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Table 2 (*continued*)

Therapeutic agent	Clinical trial ID	Number of participants	status	Additional information
			terminated, has results - poor recruitment, strong evidence from larger trials of no therapeutic benefit	compared with azithromycin, HCQ and standard treatment; combined with azithromycin
HCQ	NCT04334512	600	recruiting	combined with azithromycin
HCQ	NCT04334382	1550	recruiting	combined with azithromycin
HCQ	NCT04329832	300	active, not recruiting	combined with azithromycin
HCQ	NCT04329572	400	suspended	combined with azithromycin
HCQ	NCT04328272	75	not yet recruiting	combined with azithromycin
HCQ	NCT04323631	1116	withdrawn	compared to standard treatment
HCQ	NCT04321993	1000	recruiting	compared to baricitinib, lopinavir/ritonavir and sarilumab
HCQ	NCT04342169	400	recruiting	–
HCQ	NCT04341727	500	suspended	compared to azithromycin and chloroquine
HCQ	NCT04341493	86	terminated	compared to nitazoxanide
HCQ	NCT04334967	1250	suspended	compared to standard treatment
HCQ	NCT04333654	210	terminated	compared to standard treatment
HCQ (Self et al., 2020)	NCT04332991	510	completed, has results	–
HCQ	NCT04321616	700	recruiting	compared to remdesivir and standard treatment
HCQ + IFN β-1b + Lopinavir/ Ritonavir	IRCT20100228 003449N27	30	completed	–
HCQ + IFN β-1b + Lopinavir/ Ritonavir	IRCT20100228 003449N28	30	completed, has results (Effat et al., 2021)	doi: 10.1128/AAC.01061−20
HCQ + Lopinavir/Ritonavir	JPRN jRCTs031190227	50	completed	–
HCQ + Lopinavir/Ritonavir + Sofosbuvir/Ledipasvir	IRCT20100228 003449N29	50	completed	–
HCQ + Camostat Mesylate	NCT04338906	334	withdrawn	–
Hyperimmune Anti SARS-CoV-2 serum	NCT04913779	200	recruiting	compared to placebo
Ibuprofen	NCT04334629	230	recruiting	compared to standard of care
Ifenprodil (NP-120)	NCT04382924	168	completed	compared to standard of care
IFN α	ChiCTR2000029496	90	recruiting	compared to lopinavir/ritonavir; combined with lopinavir/ ritonavir
IFN α	ChiCTR2000029600	90	recruiting	compared to lopinavir/ritonavir and favipiravir
IFN α	ChiCTR2000029638	100	recruiting	compared to rSIFN-co
IFN α	NCT04291729	11	completed	compared to darunavir/ritonavir, lopinavir/ritonavir and peginterferon α-2a
IFN α-1b	ChiCTR2000029989	300	not yet recruiting	–
IFN α-1b	NCT04293887	328	not yet recruiting	compared to standard treatment
IFN α-1b + Lopinavir/Ritonavir + Ribavirin	ChiCTR2000029387	108	recruiting	–
IFN α-2b	NCT04273763	60	active, not recruiting	combined with bromohexine, favipiravir and umifenovir
IFNα-2b + Lopinavir/Ritonavir	ChiCTR2000030166	20	not yet recruiting	–
IFN β-1a	NCT04492475	969	completed	combined with remdesivir; compared to placebo
IFN β-1a	NCT04350671	40	recruiting	combined with lopinavir/ritonavir + HCQ, compared with lopinavir/ritonavir + HCQ
IFN β-1a	2020−001023-14 (EU-CTR)	400	completed, has results (Monk et al., 2021)	–
IFN β-1a	NCT04343768	60	completed	compared to HCQ + lopinavir / ritonavir and IFN β-1b; combined with HCQ + lopinavir / ritonavir
IFN β-1b	NCT04343768	60	completed	compared to HCQ + lopinavir / ritonavir and IFN β-1a; combined with HCQ + lopinavir / ritonavir
IFN β-1b + Ribavirin	NCT04276688	70	completed	combined with lopinavir/ritonavir
IFN α and Lopinavir/Ritonavir	NCT04251871	150	recruiting	–
IFN α and Lopinavir/Ritonavir	NCT04275388	348	not yet recruiting	–
IFX-1	NCT04333420	130	recruiting	compared to standard treatment
Imatinib	NCT04394416	204	recruiting	compared to placebo
Imatinib	NCT04422678	30	not yet recruiting	compared to standard of care
Imatinib	NCT04422678	30	not yet recruiting	compared to standard of care
IMU-838	NCT04379271	223	completed	compared to placebo
INB03	NCT04370236	366	recruiting	compared to placebo
Infliximab	NCT04593940	2160	recruiting	combined with remdesivir and standard of care; compared to abatacept, ceniciviroc, standard of care
INM005	NCT04494984	242	completed	compared to placebo
Interleukin-2	ChiCTR2000030167	80	not yet recruiting	compared to standard treatment
Isavuconazole	NCT04707703	162	recruiting	compared to placebo
Isotretinoin	NCT04361422	300	not yet recruiting	compared to standard of care
Isotretinoin	NCT04353180	10,000	not yet recruiting	compared to standard of care
Ivermectin	NCT04523831	400	completed	combined with doxycycline; compared to standard of care
Ivermectin	NCT04920942	500	recruiting	compared to standard of care
Ivermectin	NCT04646109	66	completed	compared to standard of care
Ivermectin	NCT04729140	150	recruiting	combined with doxycycline; compared to placebo
Ivermectin	NCT04681053	80	recruiting	compared to standard of care
Ivermectin	NCT04739410	50	completed	compared to standard of care
Ivermectin	NCT04937569	1644	not yet recruiting	compared to standard of care
Ivermectin	NCT04885530	15,000	recruiting	compared to fluvoxamine, fluticasone, placebo

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Table 2 (*continued*)

Therapeutic agent	Clinical trial ID	Number of participants	status	Additional information
Ivermectin	NCT04746365	300	completed	compared to HCQ, placebo
Ivermectin	NCT04944082	60	not yet recruiting	combined with remdesivir; compared to remdesivir
Ivermectin	NCT04391127	108	completed	monotherapy or combined with HCQ; compared to placebo
Ivermectin	NCT04703608	1200	recruiting	compared to ASA, placebo
Ivermectin	NCT04834115	400	recruiting	compared to placebo
Ivermectin	NCT04435587	80	recruiting	compared to darunavir/ritonavir + HCQ
Ivermectin	NCT04445311	100	recruiting	compared to standard of care
Ivermectin	NCT04403555	160	recruiting	compared to standard of care
Ivermectin	NCT04351347	300	recruiting	compared to standard of care
Ivermectin	NCT04529525	501	completed	compared to placebo
Ivermectin	NCT04405843	476	completed	compared to placebo
Ivermectin	NCT04959786	100	recruiting	combined with ribavirin, nitazoxanide, Zinc; compared to standard of care
Ivermectin	NCT04716569	150	recruiting	compared to standard of care
Ivermectin	NCT04951362	117	recruiting	compared to placebo
Ivermectine	NCT04343092	50	completed, has results	combined with HCQ; compared to placebo
IVIG	NCT04500067	76	completed	compared to standard of care
IVIG	NCT04350580	146	completed	compared to placebo
IVIG	NCT04546581	593	active	combined with remdesivir; compared to placebo + remdesivir
IVIG	NCT04842435	376	recruiting	compared to placebo
IVIG	NCT04891172	310	recruiting	compared to standard of care
Ixekizumab	NCT04724629	60	recruiting	compared to adesleukin, colchicine, standard of care
Ixekizumab	ChiCTR2000030703	40	recruiting	compared to antiviral therapy; combined with antiviral therapy
Leflunomide (Wang et al., 2020b)	ChiCTR2000030058	200	completed, has results	compared to standard treatment
Lenalidomide	NCT04361643	120	not yet recruiting	compared to placebo
Lenlizumab	NCT04351152	520	active	compared to standard of care
Leronlimab	NCT04901689	306	not yet recruiting	compared to placebo
Leronlimab	NCT04343651	70	active, not recruiting	–
Levamisole	NCT04331470	30	recruiting	compared to standard treatment; combined with budesonide, formoterol and hydroxychloroquine + lopinavir/ritonavir
Levilimab	NCT04397562	206	completed	compared to placebo
Lianhua Qingwen	NCT04433013	300	not yet recruiting	compared to placebo
Lidocaine	NCT04609865	100	recruiting	compared to placebo
Lilly Bamlanivimab	NCT04790786	5000	recruiting	compared to regeneron casirivimab + imdevimab, Lilly Bamlanivimab + etesevimab, sotrovimab
Lipid Emulsion Infusion	NCT04957940	90	recruiting	compared to placebo
Liposomal Lactoferrin	NCT04475120	92	completed	compared to standard of care
Lopinavir / Ritonavir	NCT04738045	90	recruiting	combined with remdesivir; compared to remdesivir
Lopinavir / Ritonavir	NCT04466241	294	recruiting	monotherapy or combined with telmisartan, atorvastatin
Lopinavir / Ritonavir	NCT04403100	1968	recruiting	monotherapy or combined with HCQ; compared to HCQ, placebo
Lopinavir / Ritonavir	NCT04381936	45,000	recruiting	compared to corticosteroid, HCQ, azithromycin, convalescent plasma, tocilizumab, immunoglobulin, neutralizing antibodies, ASA, colchicine, baricitinib, anakinra, dimethyl fumarate, empagliflozin
Lopinavir/Ritonavir	2020−000936-23 (EU-CTR)	3000	ongoing	compared to IFN β-1a and remdesivir
Lopinavir/Ritonavir (Cao et al., 2020)	ChiCTR2000029308	160	completed, has results	compared to standard treatment
Lopinavir/Ritonavir	ChiCTR2000029400	60	recruiting	–
Lopinavir/Ritonavir (Zheng et al., 2020)	ChiCTR2000029496	90	completed, has results	compared to IFN α; combined with IFN α
Lopinavir/Ritonavir	ChiCTR2000029539	328	recruiting	compared to standard treatment
Lopinavir/Ritonavir	ChiCTR2000029548	30	not yet recruiting	compared to baloxavir marboxil and favipiravir
Lopinavir/Ritonavir	ChiCTR2000029573	480	recruiting	combined with IFN-α and umifenovir
Lopinavir/Ritonavir	ChiCTR2000029600	90	recruiting	compared to favipiravir; combined with IFN α
Lopinavir/Ritonavir	ChiCTR2000029609	200	not yet recruiting	compared to chloroquine
Lopinavir/Ritonavir	ChiCTR2000030187	60	recruiting	compared to standard treatment
Lopinavir/Ritonavir	ChiCTR2000030218	80	recruiting	–
Lopinavir/Ritonavir	NCT04252885	125	completed	compared to standard treatment and umifenovir
Lopinavir/Ritonavir	NCT04255017	400	recruiting	compared to oseltamivir and umifenovir
Lopinavir/Ritonavir	NCT04261907	160	not yet recruiting	compared to ASC09
Lopinavir/Ritonavir	NCT04291729	11	completed	compared to darunavir/ritonavir, IFN α and peginterferon α-2a
Lopinavir/Ritonavir	NCT04315948; 2020−000936-23 (EU-CTR)	3100	active, not recruiting	compared to hydroxychloroquine and remdesivir; combined with IFN β-1a
Lopinavir/Ritonavir	NCT04330690	440	recruiting	compared to standard care
Lopinavir/Ritonavir	NCT04321993	1000	recruiting	compared to baricitinib, hydroxychloroquine and sarilumab
Losartan	NCT04606563	1372	recruiting	compared to standard of care

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Table 2 (*continued*)

Therapeutic agent	Clinical trial ID	Number of participants	status	Additional information
Losartan	NCT04328012	100	recruiting	compared to placebo
Losartan (Geriak et al., 2021)	NCT04340557	200	completed, has results	–
Losmapimod	NCT04511819	410	active	compared to placebo
LY3127804	NCT04342897	200	terminated	–
LY3819253	NCT04501978	10,000	recruiting	compared to remdesivir, VIR-7831, BRII-196/BRII-198, AZD7442, MP0420, placebo
LY3819253	NCT04427501	577	recruiting	monotherapy or combined with LY3832479; compared to placebo
MAD0004J08	NCT04952805	800	recruiting	compared to placebo
Mavrilimumab	NCT04447469	588	recruiting	compared to placebo
Mefloquine	NCT04347031	320	completed	monotherapy or combined with azithromycin +/- tocilizumab; compared to HCQ; HCQ + azithromycin +/- tocilizumab
Meplazumab	NCT04275245	28	completed	–
Mesenchymal Stem Cells	NCT04366063	60	recruiting	compared to standard of care
Mesenchymal Stromal Cells	NCT04371393	223	active	compared to placebo
Metenkefalin	NCT04374032	120	completed	combined with tridecactide; compared to standard of care
Metformin	NCT04510194	1160	recruiting	combined and compared with ivermectin, fluvoxamine, placebo
Methylprednisolone	NCT04673162	260	not yet recruiting	compared to standard of care
Methylprednisolone	NCT04438980	72	completed	compared to placebo
Methylprednisolone	NCT04636671	680	recruiting	compared to dexamethasone
Methylprednisolone	NCT04244591	80	completed	compared to standard of care
Methylprednisolone	NCT04263402	100	recruiting	–
Methylprednisolone	ChiCTR2000029386	48	recruiting	compared to standard treatment
Methylprednisolone	ChiCTR2000029656	100	not yet recruiting	compared to standard treatment
Methylprednisolone	NCT04244591	80	completed	compared to standard treatment
Methylprednisolone	NCT04273321	400	completed	compared to standard treatment
Methylprednisolone	NCT04323592	104	completed, has results	compared to standard treatment
Molixan	NCT04780672	330	recruiting	compared to placebo
Molnupiravir	NCT04575584	304	active	compared to placebo
Molnupiravir	NCT04575597	1850	recruiting	compared to placebo
Montelukast	NCT04389411	600	not yet recruiting	compared to placebo
MultiStem	NCT04367077	400	recruiting	compared to placebo
NA-831	NCT04452565	525	recruiting	monotherapy or combined with atazanavir or dexamethasone; compared to atazanavir + dexamethasone
N-acetylcysteine	NCT04792021	60	recruiting	compared to standard of care
Nafamostat Mesilate	NCT04390594	186	recruiting	compared to standard of care
Nafamostat Mesilate	NCT04483960	2400	recruiting	compared to standard of care
Nafamostat Mesilate	NCT04352400	256	recruiting	compared to placebo
Nafamostat Mesilate	NCT04473053	60	recruiting	compared to TD139, standard of care
Nangibotide	NCT04429334	730	recruiting	compared to placebo
Naproxen	NCT04325633	584	terminated	compared to standard treatment
Neurokinin-1 Receptor	NCT04468646	100	recruiting	compared to placebo
Niagen	NCT04809974	100	recruiting	compared to placebo
Niclosamide	NCT04558021	200	recruiting	compared to placebo
Niclosamide	NCT04603924	436	recruiting	compared to placebo
Nintedanib	NCT04541680	250	recruiting	compared to placebo
Nintedanib	NCT04619680	120	recruiting	compared to placebo
Nitazoxanide	NCT04486313	1092	completed	compared to placebo
Nitazoxanide	NCT04423861	380	not yet recruiting	compared to placebo
Nitazoxanide	NCT04392427	100	not yet recruiting	combined with ribavirin and ivermectin; compared to standard of care
Nitazoxanide	NCT04382846	160	recruiting	compared to standard of care
Nitazoxanide	NCT04523090	440	recruiting	compared to placebo
Nitazoxanide	NCT04463264	135	recruiting	compared to placebo
Nitazoxanide	NCT04920838	600	recruiting	combined with ciclesonide; compared to paracetamol, telmisartan
Nitazoxanide	NCT04341493	86	terminated	compared to hydroxychloroquine
Nivolumab	NCT04343144	92	not yet recruiting	compared to standard treatment
Novaferon	NCT04669015	914	recruiting	compared to placebo
Octagam	NCT04400058	208	completed	compared to placebo
Octagam	NCT04411667	34	completed	compared to standard of care
Omega 3	NCT04553705	200	recruiting	combined with sativa oil, Indian Costus, quinine pills, anise seed capsules
Opaganib	NCT04467840	475	completed	compared to placebo
Oseltamivir	NCT04255017	400	recruiting	compared to lopinavir/ritonavir and umifenovir
Oseltamivir	NCT04261270	60	recruiting	compared to ASC09 and ritonavir
Oseltamivir	NCT04303299	80	recruiting	compared to favipiravir, lopinavir/ritonavir and standard treatment; combined with chloroquine, darunavir/ritonavir and lopinavir/ritonavir
Ozone therapy	NCT04359303	50	not yet recruiting	compared to standard of care
Ozone therapy	NCT04370223	208	not yet recruiting	compared to standard of care
P2Et	NCT04410510	100	recruiting	compared to placebo
Pacritinib	NCT04404361	200	active	compared to placebo

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Table 2 (*continued*)

Therapeutic agent	Clinical trial ID	Number of participants	status	Additional information
Palmitoylethanolamide	NCT04568876	40	recruiting	compared to standard of care
PD-1 monoclonal antibody	ChiCTR2000030028	40	not yet recruiting	compared to standard treatment
PD-1 monoclonal antibody	NCT04268537	120	not yet recruiting	compared to standard treatment and thymosin
Peginterferon Lambda-1a	NCT04331899	120	completed, has results	doi: 10.1038/s41467−021-22177−1
Peginterferon α-2a	NCT04291729	11	completed	compared to darunavir/ritonavir, IFN α and lopinavir/ritonavir
Piclidenoson	NCT04333472	40	recruiting	compared to standard treatment
Pioglitazone	NCT04535700	76	recruiting	compared to standard of care in DM2 patients
Pirfenidone	NCT04282902	294	recruiting	compared to standard of care
Plitidepsin	NCT04784559	609	recruiting	combined with dexamethasone; compared to remdesivir + dexamethasone
Polyinosinic polycytidylic acid	ChiCTR2000029776	40		compared to standard treatment
Propolis extract	NCT04800224	200	recruiting	compared to placebo
Proxalutamide	NCT04869228	724	not yet recruiting	compared to placebo
Proxalutamide	NCT04853134	200	active	compared to standard of care
Proxalutamide	NCT04728802	645	completed	compared to placebo
Proxalutamide	NCT04870606	668	recruiting	compared to placebo
Psidii guava	NCT04810728	90	completed	compared to standard of care
PTC299	NCT04439071	380	recruiting	compared to placebo
PTC299	NCT04439071	380	recruiting	compared to standard of care
PUL-042	NCT04312997	100	completed	–
PVP-I	NCT04872686	798	recruiting	compared to placebo
Pyridostigmine Bromide	NCT04343963	436	recruiting	compared to placebo
Pyronaridine-artesunate	NCT04701606	402	recruiting	compared to placebo
Quercetin	NCT04468139	60	recruiting	combined with Zinc, Vitamin C, bromelain; single group assessment
Quercetin phytosome	NCT04578158	152	completed	compared to standard of care
Radiation Therapy	NCT04433949	52	recruiting	compared to standard of care
Ramdicivir	NCT04693026	150	recruiting	combined with baricitinib; compared to remdesivir + tocilizumab
Ravulizumab	NCT04390464	1167	recruiting	compared to baricitinib, standard of care
Ravulizumab	NCT04369469	270	active	compared to standard of care
REGN10933+REGN10987	NCT04425629	6420	recruiting	compared to placebo
REGN10933+REGN10987	NCT04452318	3750	active	compared to placebo
Remdesivir	NCT04843761	640	recruiting	compared to aviptadil, steroids, placebo
Remdesivir	NCT04853901	77	completed	compared to standard of care
Remdesivir	NCT04647669	100	not yet recruiting	compared to acalabrutinib, IFN β-1a, standard of care
Remdesivir	NCT04779047	150	recruiting	compared to HCQ, tocilizumab, lopinavir / ritonavir, ivermectin
Remdesivir	NCT04745351	1116	recruiting	compared to standard of care
Remdesivir	NCT04610541	2000	active	single group assignment
Remdesivir	NCT04431453	52	recruiting	single group assignment
Remdesivir	NCT04575064	400	active	compared to standard of care
Remdesivir	NCT04345419	200	completed	compared to standard of care
Remdesivir	NCT04315948	2416	active	compared to lopinavir/ritonavir, lopinavir / ritonavir + IFN β-1a, HCQ, AZD7442, standard of care
Remdesivir	2020−000936-23 (EU-CTR)	3000	ongoing	compared to IFN β-1a and lopinavir/ritonavir
Remdesivir	NCT04252664	308	suspended	–
Remdesivir	NCT04257656	453	terminated	–
Remdesivir (Beigel et al., 2020)	NCT04280705	394	completed, has results	–
Remdesivir (Spinner et al., 2020)	NCT04292730; 2020−000842-32 (EU-CTR)	600	completed, has results	compared to standard treatment
Remdesivir (Goldman et al., 2020)	NCT04292899; 2020−000841-15 (EU-CTR)	400	completed, has results	compared to standard treatment
Remdesivir	NCT04315948	3100	active, not recruiting	compared to hydroxychloroquine, IFN β-1a and lopinavir/ritonavir
Remdesivir	NCT04321616	700	recruiting	compared to hydroxychloroquine and standard treatment
Remdesivir + Baricitinib	NCT04832880	4000	not yet recruiting	combined with dexamethasone; compared to remdesivir + dexamethasone, baricitinib + dexamethasone, dexamethasone
Remdesivir + Tocilizumab	NCT04678739	205	completed	compared to standard of care
Reparixin	NCT04878055	312	recruiting	compared to placebo
Reparixin	NCT04878055	312	recruiting	compared to placebo
RESP301	NCT04460183	300	recruiting	compared to standard of care
RhACE2 APN01	NCT04335136	200	completed	–
rhG-CSF (Cheng et al., 2021)	ChiCTR2000030007	200	completed, has results	compared to standard treatment
Ribavirin	ChiCTR2000030922	30	recruiting	combined with IFN α-2a and umifenovir
Ritonavir	ChiCTR2000030113	20	recruiting	compared to favipiravir
RO7496998	NCT04889040	1386	recruiting	compared to placebo
RPH-104	NCT04380519	372	completed	compared to olokizumab, placebo
rSIFN-co	ChiCTR2000029638	100	recruiting	compared to IFN α
Ruconest	NCT04705831	40	recruiting	compared to placebo

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Table 2 (*continued*)

Therapeutic agent	Clinical trial ID	Number of participants	status	Additional information
Ruxolitinib	NCT04362137	432	completed	compared to placebo
Ruxolitinib	NCT04338958	200	recruiting	–
Ruxolitinib	NCT04331665	64	completed	–
Sargramostim	NCT04326920	80	completed	compared to standard of care
Sargramostim	NCT04642950	60	recruiting	compared to placebo
Sarilumab (Lescure et al., 2021a)	NCT04327388	300	completed, has results	doi: 10.1016/S2213−2600(21)00099−0
Sarilumab	NCT04322773	200	terminated	compared to standard treatment and tocilizumab
Sarilumab	NCT04341870	60	suspended	combined with azithromycin and HCQ; compared with sarilumab
Sarilumab	NCT04315298	400	completed	–
Sarilumab	NCT04321993	1000	recruiting	compared to baricitinib, HCQ, and lopinavir/ritonavir
SARS-CoV-2 Convalescent Plasma	NCT04372979	80	recruiting	compared to standard plasma
SARS-CoV-2 Convalescent Plasma	NCT04432103	36	not yet recruiting	parallel assignment - two groups depending on the stage of the disease
SCTA01	NCT04644185	795	recruiting	compared to placebo
Sildenafil	NCT04304313	10	recruiting	single group assignment
Sildenafil	NCT04304313	10	recruiting	–
Siltuximab	NCT04329650	100	recruiting	compared to methylprednisolone
Silymarin	NCT04816682	30	recruiting	compared to standard of care
Silymarin	NCT04394208	50	recruiting	compared to placebo
Sirolimus	NCT04948203	60	recruiting	parallel assignment - varying doses of sirolimus
Sirolimus	NCT04341675	30	recruiting	–
SNG001	NCT04732949	610	recruiting	compared to placebo
Sodium Pyruvate	NCT04824365	60	recruiting	compared to placebo
Sofosbuvir	NCT04535869	50	recruiting	combined with daclatasvir
Sofosbuvir	NCT04460443	60	recruiting	combined with ledipsavir; compared to sofosbuvir + daclatasvir, standard of care
Sofosbuvir	NCT04497649	100	recruiting	combined with daclatasvir; compared to standard of care
Sofosbuvir + Daclatasvir	NCT04773756	54	completed	single group assignment
Sofosbuvir + Ledipasvir	NCT04530422	250	completed	compared to oseltamivir + HCQ + azithromycin
Sofosbuvir + Ledipasvir	NCT04498936	240	completed	compared to nitazoxanide, standard of care
Sofosbuvir + Ledipasvir	NCT04460443	60	recruiting	compared to sofosbuvir + daclatasvir, standard of care
Sofosbuvir/Daclatasvir (Simmons et al., 2021)	IRCT20200128046294N2	70	completed; has results	compared to standard treatment
Sotrovimab	NCT04913675	1020	recruiting	i.v. administration versus i.m. administration
Spironolactone	NCT04424134	80	recruiting	combined with bromhexine; compared to standard of care
Spironolactone	NCT04826822	440	recruiting	combined with dexamethasone; compared to standard of care
Suleoxide	NCT04483830	243	completed	compared to placebo
Tacrolimus	NCT04341038	84	recruiting	compared to standard treatment; combined with methylprednisolone
Telmisartan	NCT04355936	400	completed	compared to standard of care
Telmisartan	NCT04356495	820	recruiting	compared to ciclesonide, IFN β-1b, vitamins
Tenofovir	NCT04685512	60	completed	combined with emtricitabine; compared to standard of care
Tetrandrine	NCT04308317	60	recruiting	compared to standard of care
Therapeutic Plasma Exchange	NCT04973488	38	completed	compared to standard of care
Thymosin	ChiCTR2000029541	100	not yet recruiting	combined with darunavir/cobicistat or lopinavir/ritonavir
Thymosin	ChiCTR2000029806	120	recruiting	compared to camrelizumab and conventional treatment
Tigerase	NCT04459325	100	completed	compared to standard of care
TJ003234	NCT04341116	144	recruiting	–
Tocilizumab	NCT04577534	88	completed	compared to standard of care
Tocilizumab	NCT04730323	93	completed	compared to methylprednisolone + standard of care
Tocilizumab	NCT04600141	308	recruiting	combined with heparin
Tocilizumab	NCT04377750	500	recruiting	compared to placebo
Tocilizumab	NCT04412772	300	recruiting	compared to placebo
Tocilizumab	NCT04372186	388	active	compared to placebo
Tocilizumab	NCT04409262	649	completed	combined with remdesivir; compared to remdesivir + placebo
Tocilizumab	NCT04356937	243	completed	compared to placebo
Tocilizumab	ChiCTR2000029765	188	recruiting	compared to standard treatment
Tocilizumab	ChiCTR2000030196	60	not yet recruiting	–
Tocilizumab	ChiCTR2000030442	100	not yet recruiting	–
Tocilizumab	NCT04310228	150	recruiting	compared to favipiravir; combined with favipiravir
Tocilizumab	NCT04315480	30	active, not recruiting	–
Tocilizumab	NCT04317092	400	active, not recruiting	–
Tocilizumab	NCT04339712	20	completed	compared to anakinra
Tocilizumab	NCT04331808	240	active, not recruiting	–
Tocilizumab	NCT04322773	200	terminated	compared to sarilumab and standard treatment
Tocilizumab	NCT04335305	24	recruiting	compared to standard treatment; combined with pembrolizumab
Tocilizumab	NCT04335071	100	terminated	–
Tocilizumab	NCT04332913	30	recruiting	–
Tocilizumab	NCT04332094	276	recruiting	compared with azithromycin + hydroxychloroquine; combined with azithromycin + HCQ

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Table 2 (*continued*)

Therapeutic agent	Clinical trial ID	Number of participants	status	Additional information
Tocilizumab	NCT04331795	50	recruiting	–
Tocilizumab	NCT04330638	342	active, not recruiting	compared with anakinra and siltuximab; combined with anakinra and siltuximab
Tocilizumab (Rosas et al., 2021)	NCT04320615	330	completed, has results	–
Tofacitinib	NCT04332042	50	not yet recruiting	–
Tradipitant	NCT04326426	300	enrolling by invitation	–
Traditional Chinese Medicine	NCT04323332	50	not yet recruiting	compared to standard of care
Tranexamic acid	NCT04338126	60	withdrawn	–
Tranexamic acid	NCT04338074	100	terminated (lack of recruitment)	–
Tranilast	ChiCTR2000030002	60	recruiting	compared to standard treatment
Triazavirin	ChiCTR2000030001	240	recruiting	compared to standard treatment
Triazavirin (Riamilovir)	NCT04581915	420	recruiting	compared to placebo
TY027	NCT04649515	1305	recruiting	compared to placebo
Ulinastatin	ChiCTR2000030779	100	recruiting	compared to standard treatment
Umifenovir	NCT04350684	40	recruiting	combined with IFN β-1a + lopinavir / ritonavir + HCQ + standard of care; compared to IFN β-1a + lopinavir / ritonavir + HCQ + standard of care
Umifenovir	ChiCTR2000029573	480	recruiting	combined with IFN α and lopinavir/ritonavir
Umifenovir	ChiCTR2000029621	380	recruiting	compared to standard treatment
Umifenovir	ChiCTR2000029993	40	recruiting	–
Umifenovir (Chen et al., 2020)	ChiCTR2000030254	240	completed, has results	compared to favipiravir
Umifenovir	NCT04252885	125	completed	compared standard treatment and tolopinavir/ritonavir
Umifenovir	NCT04254874	100	recruiting	combined with peginterferon α-2a
Umifenovir	NCT04255017	400	recruiting	compared to lopinavir/ritonavir and oseltamivir
Umifenovir	NCT04273763	60	active, not recruiting	combined with bromohexine, favipiravir and IFN α-2b
Upamostat	NCT04723537	310	recruiting	compared to placebo
Valsartan	NCT04335786	651	recruiting	compared to placebo
Valsartan	NCT04335786	651	recruiting	–
VIR-7831	NCT04545060	1360	active	compared to placebo
Vitamin C	NCT04401150	800	recruiting	compared to placebo
Vitamin D	NCT04411446	1264	recruiting	compared to placebo
Vitamin D	NCT04536298	2700	recruiting	compared to placebo
Vitamin D	NCT04641195	700	recruiting	monotherapy or combined with Zinc; compared to Zinc, placebo
Vitamin D	NCT04385940	64	recruiting	high dose vitamin D compared to low dose vitamin D
Vitamin D	NCT04636086	100	recruiting	compared to placebo
Vitamin D	NCT04552951	80	recruiting	compared to standard of care
Vitamin D	NCT04780061	200	recruiting	compared to vitamin C + Zinc, vitamin K2 + D, triglyceride oil, microcrystalline cellulose
Vitamin D	NCT04579640	6200	active	compared to standard of care
Vitamin D	NCT04482673	140	recruiting	compared to standard of care
Vitamin D	NCT04502667	40	recruiting	compared to standard of care
Vitamin D	NCT04386850	1500	recruiting	compared to placebo
Vitamin D	NCT04344041	260	completed	high dose vitamin D compared to low dose vitamin D
Vitamin D	NCT04621058	108	recruiting	compared to placebo
XAV-19	NCT04928430	722	recruiting	compared to placebo
XC221	NCT04940182	274	recruiting	compared to placebo
XC221	NCT04487574	118	completed	compared to placebo
Zafirlukast	NCT04871828	66	recruiting	compared to placebo
Zavegepant (BHV-3500)	NCT04346615	120	recruiting	compared to placebo
Zinc	NCT04447534	200	recruiting	combined with Chloroquine; compared to Chloroquine
Zinc	NCT04621461	3	completed	compared to placebo

Legend: ACE-I – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers; ASA – acetylsalicylic acid, aspirin; HCQ – hydroxychloroquine; IFN – interferon.

the baricitinib-arm compared to the 17.9 % (14/78) in the control-arm in week 1 ($p = 0.019$; 95 % CI: 0.0092 – 0.6818), and week 2 ($p < 0.0001$; 95 % CI: 0.0038 – 0.2624). Discharge rate was significantly higher in the baricitinib-arm at week 1 [9.7 % (11/113) vs. 1.3 % (1/78); $p = 0.039$; 95 % CI: 1.41–90.71], and at week 2 [77.8 % (88/113) vs. 12.8 % (10/78); $p < 0.0001$; 95 % CI: 10.79–51.74] (Cantini et al., 2020). In a randomized trial, Marconi et al., demonstrated that baricitinib may be an important drug that can be used in patients hospitalized for COVID-19 (Marconi et al., 2021). The 60-day all-cause mortality was 10 % (= 79) for baricitinib and 15 % (n = 116) for placebo (HR 0.62 [95 % CI 0.47–0.83]; $p = 0.0050$). The use of this drug did not significantly increase the side effects (Marconi et al., 2021). The authors of this study recommend the use baricitinib in hospitalized patients diagnosed with COVID-19 with moderate and severe disease.

3.4. Tofacitinib

Tofacitinib is a potent and selective inhibitor of the JAK family of kinases. Tofacitinib has been shown to inhibit the activity of JAK1, JAK2, and JAK3, and to a lesser extent tyrosine-protein 2 kinases (TyK2). In human cells, tofacitinib inhibits the signaling of heterodimeric cytokine receptors which bind JAK3 and/or JAK1, and that possess greater functional selectivity than that of cytokine receptors that signal through JAK2 kinase pairs. Inhibition of JAK1 and JAK3 kinases by tofacitinib attenuates interleukin signaling (IL-2, IL-4, IL-6, IL-7, IL-9, IL-15, and IL-21), as well as interferon type I and type II signaling, resulting in modulation of the immune response (Maeshima et al., 2012).

Guimarães *et al.,* assessed the efficacy and safety of tofacitinib in patients hospitalized for coronavirus pneumonia. Two groups of adult patients (n = 289 in total) with COVID-19 pneumonia were randomized

Table 3
COVID-19 – summary of World Health Organization (WHO), National Institute of Health, and Infectious Diseases Society of America guidelines (COVID-19 Treatment Guidelines Panel, 2021; Organization, 2021; Bhimraj et al., 2021).

Drug	WHO	Dose	Patient condition
Baricitinib	N/A	4 mg daily for 14 days or until hospital discharge (whichever is first)	Patients with SpO2 ≤ 94 % on room air and CRP ≥ 75 mg/L, and no invasive mechanical ventilation Patients with contraindications to receive dexamethasone or other corticosteroids
Dexamethasone	Recommended	6 mg iv or per os daily for 10 days or until hospital discharge (whichever is first)	Patients with SpO2 ≤ 94 % on room air
Neutralizing antibodies (casirivimab/ imdevimab, or sotrovimab)	N/A	–	COVID-19 at high risk for progression
Remdesivir	Not recommended	200 mg iv – 1st day one 100 mg iv daily - days 2–5	Patients with SpO2 ≤ 94 % on room air
Tocilizumab	Recommended	4 – 8 mg/kg iv (single dose)	Patients with SpO2 ≤ 94 % on room air and CRP ≥ 75 mg/L
HCQ	Not recommended	N/A	N/A

in a 1:1 ratio, receiving either 10 mg of tofacitinib or a placebo twice daily for up to 14 days or until hospital discharge. Efficacy was assessed after 28 days and examined the death or respiratory failure rate. Furthermore, 89.3 % of patients were receiving glucocorticoids during their hospitalization. The cumulative incidence of death or respiratory failure up to day 28 was 18.1 % in the tofacitinib group and 29.0 % in the placebo group (hazard ratio (HR) = 0.63; 95 % CI: 0.41 – 0.97; p = 0.04). By day 28, death from any cause had occurred in 2.8 % of patients in the tofacitinib group and in 5.5 % of patients in the placebo group (HR = 0.49; 95 % CI: 0.15–1.63). The authors summarized the study by stating that among patients hospitalized with COVID-19 pneumonia, tofacitinib led to a decrease in the risk of death or respiratory failure by day 28 in comparison with a placebo (Gunay et al., 2021). According to the authors, the use of tofacitinib in hospitalized patients diagnosed with COVID-19 may be considered.

3.5. *Application of autophagy and UPR in targeting SARS-CoV-2 infection*

The endoplasmic reticulum (ER) is the site of both protein translation and protein folding (Sureda et al., 2020). However, if the protein load that is shuffled into the ER exceeds its folding capacity, there is an accumulation of unfolded proteins which triggers the ER stress response, and activates a pathway known as the unfolded protein response (UPR) (Almanza et al., 2019). UPR aims to improve ER folding capacity by reducing global protein synthesis and inducing molecular chaperone expression (Hombach-Klonisch et al., 2018). However, if ER stress is not resolved, UPR directs the cell towards programmed cell death (Mehrbod et al., 2019).

Multiple studies have shown that CoV replication in the cytoplasm directly induces ER stress, leading to the activation of UPR in infected cells. As an intricate interplay between UPR and the inflammatory response, apoptosis, autophagy, and innate immunity exists, ER stress can significantly affect the patient's antiviral response (Fung and Liu, 2019; Shi et al., 2019). Recent evidence suggests that upon coronavirus infection, ER stress and UPR are induced by excessive synthesis, modification, and folding of viral proteins that results in ER membrane restructuring and its subsequent exhaustion due to continued formation of new virions (Fung et al., 2014; Fung and Liu, 2014). Moreover, some members of the *coronaviridae* family are capable of utilizing certain aspects of UPR to overcome protein translation shutdown and ensure the production of their own proteins (Fung et al., 2016). Moreover, in severe COVID-19 cases, hypoxemia may trigger a response from both mitochondria and ER, which is directed towards restoring oxygen level and promoting cell survival (Bartoszewska and Collawn, 2020). However, if this state persists, the role of UPR would then be altered from pro-survival to induction of apoptosis, which is possibly one of the molecular causes of organ damage in COVID-19 (Sureda et al., 2020).

Unsurprisingly, multiple therapeutic drug candidates for COVID-19 infection are autophagy modulators. It is therefore possible that the beneficial effect of these drugs is perhaps due to the over-accumulation of autophagosomes that can induce apoptotic cell death of virally infected cells (Shojaei et al., 2020). Further research exploring CoV-induced UPR could help identify novel therapeutic targets that are based directly on the pathogenesis of the disease.

Studies exploring UPR reveal that the inositol-requiring enzyme 1 (IRE1) axis is involved in the regulation of the secretome of cells via production of spliced XBP (Logue et al., 2018). Moreover, SARS-CoV activates NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasomes in macrophages as well as induces UPR through its Open Reading Frame-8b (ORF-8b) (Shi et al., 2019). The latter is involved in autophagy flux activation and cytokine processing. Hence, targeting the RNase activity of IRE1 could potentially modulate COVID-19 infection via modulation of the macrophage secretome.

In another study, SARS-CoV activated the protein kinase R-like reticulum kinase (PERK) arm of UPR, thereby increasing the phosphorylation of eukaryotic initiation factor 2 alpha (eIF2α). As PERK activation suppresses type 1 interferon signaling, it could be a potential mechanism through which innate immunity is suppressed in CoV infected cells (Minakshi et al., 2009). Therefore, PERK inhibitors could potentially aid in halting SARS-CoV-2 infection.

3.5.1. *Paxlovid*

Paxlovid is a therapeutic combination consisting of two compounds: PF-07,321,332, an oral covalent 3CL protease inhibitor of SARS-CoV-2 and ritonavir, an inhibitor of HIV-1 and HIV-2 protease. Ritonavir is also an inhibitor of cytochrome P450 3A and CYP2D6, thus inhibiting the metabolism of PF-07,321,332 and allowing the administration of a lower dose of the substance. In contrast, P-07,321,332 binds to the catalytic cysteine residue of CyS145 in all coronavirus proteases infecting humans (Mahase, 2021a).

In a recent study, the participants were randomized 1:1; half of which received paxlovid and the other half received placebo administered orally every 12 h for five consecutive days (Mahase, 2021b). The study revealed that among patients who were treated with paxlovid within three days of symptom onset, 3 out of 339 (0.8 %) participants were admitted to hospital by day 28 after randomization and no deaths were reported. In comparison, 7% (27/385) of patients who received placebo were admitted to the hospital, with seven deaths reported. The statistical significance of these results was assessed as high ($p < 0.0001$). In subjects treated within five days of symptom onset, 1% (6/607) of those treated with paxlovid were admitted to hospital by day 28 compared to 6.7 % (41/612) of patients in the placebo group. Up to day 28, no deaths were reported in the paxlovid group as compared to 10 deaths (1.6 %) in the placebo group (Mahase, 2021b).

3.5.2. *Molnupiravir*

The mechanism of action of molnupiravir (Lagevrio) is based on a novel approach to fighting viruses. The compound is converted in the

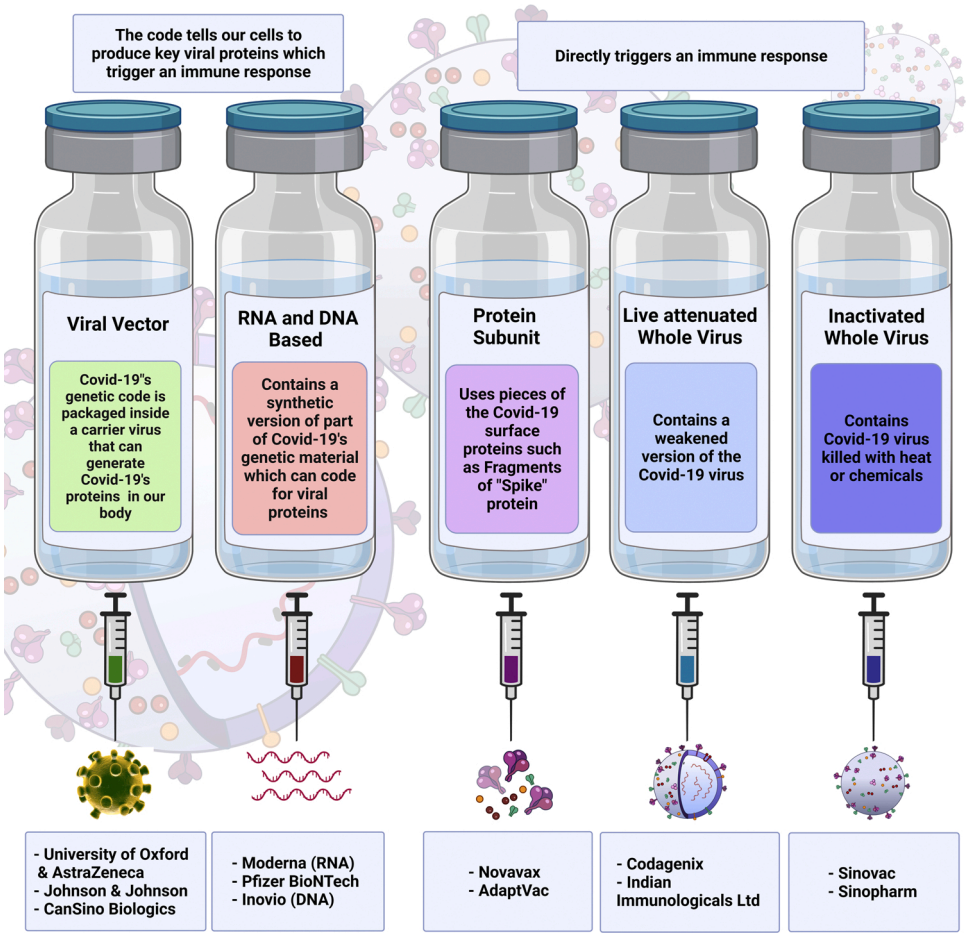

Fig. 3. Schematic representation of available anti-SARS-CoV-2 vaccines. The principle, main components and mechanism of action of each vaccine type has been explained in detail in the text.

Table 4
Efficacy of FDA Approved Vaccines Against Selected Sars-Cov2 Variants (Gubbay et al., 2021).

Virus variant			
Name of the vaccine	**Alpha Variant (B.1.1.7)**	**Beta Variant (B.1.351)**	**Delta Variant (B.1.617.2)**
Comirnaty (Pfizer BioNTech)	Vaccine effectiveness Vs symptomatic infection	Vaccine effectiveness Vs symptomatic infection	Vaccine effectiveness Vs symptomatic infection
Dose 1	95 % **CI 64**–68 %	95 % **CI 52**–67 %	~56 %
Dose 2	95 % **CI 86**–91 %	95 % **CI 69**–92 %	95 % **CI 64**–95 %
Spikevax (Moderna)	Vaccine effectiveness Vs Hospitalization rate	Vaccine effectiveness Vs Hospitalization rate	Vaccine effectiveness Vs Hospitalization rate
Dose 1	95 % **CI 80**–86 %	95 % **CI 69**–92 %	~78 %
Dose 2	95 % **CI 86**–96 %	**No information**	**No information**
Janssen COVID-19 Vaccine (Johnson & Johnson)	Vaccine effectiveness Vs symptomatic infection rate	Vaccine effectiveness Vs symptomatic infection rate	Vaccine effectiveness Vs symptomatic infection rate
Dose 1	effective according to the manufacturer	effective according to the manufacturer	effective according to the manufacturer

Legend: 95 % CI – 95 % confidence interval.

patient's body into a synthetic cytidine nucleoside. It then introduces errors into the genetic material of the viruses RNA as it replicates. The mutations lead to defective viral elements, hence neutralizing the pathogen, ultimately exerting an antiviral effect (Painter et al., 2021). Among 202 participants of a recent study, significantly lower number of participants receiving 800 mg dose of molnupiravir (1.9 %) were carried virus that could be isolated, as compared to placebo (16.7 %) at day 3 ($p = 0.02$). At day 5, virus could not be isolated from any participants receiving 400 or 800 mg molnupiravir, versus 11.1 % of those receiving placebo ($p = 0.03$). Molnupiravir was generally well tolerated, with similar adverse events across all groups (Fischer et al., 2021).

3.5.3. *Regdanvimab*

Regdanvimab (Regkirona) is a recombinant human IgG1 monoclonal antibody. The mechanism of action for regdanvimab in treating patients with SARS-CoV-2 infection is binding of regdanvimab to the receptor binding domain (RBD) of the spike(s) protein of SARS-CoV-2 with dissociation constant KD = 0.065 nM, thus, inhibiting the interaction between the SARS-CoV-2 RBD and the cellular receptor, namely the angiotensin-converting enzyme 2 (ACE2), and consequently blocking cellular entry and SARS-CoV-2 infection. Regkirona is recommended for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of their disease becoming severe (European Medicines Agency, 2021). The main study in patients with COVID-19 showed that Regkirona treatment led to fewer patients requiring hospitalizations or oxygen therapy or dying when compared with placebo. Among the patients at increased risk of their illness becoming severe, 3.1 % of patients treated with Regkirona (14 out 446)

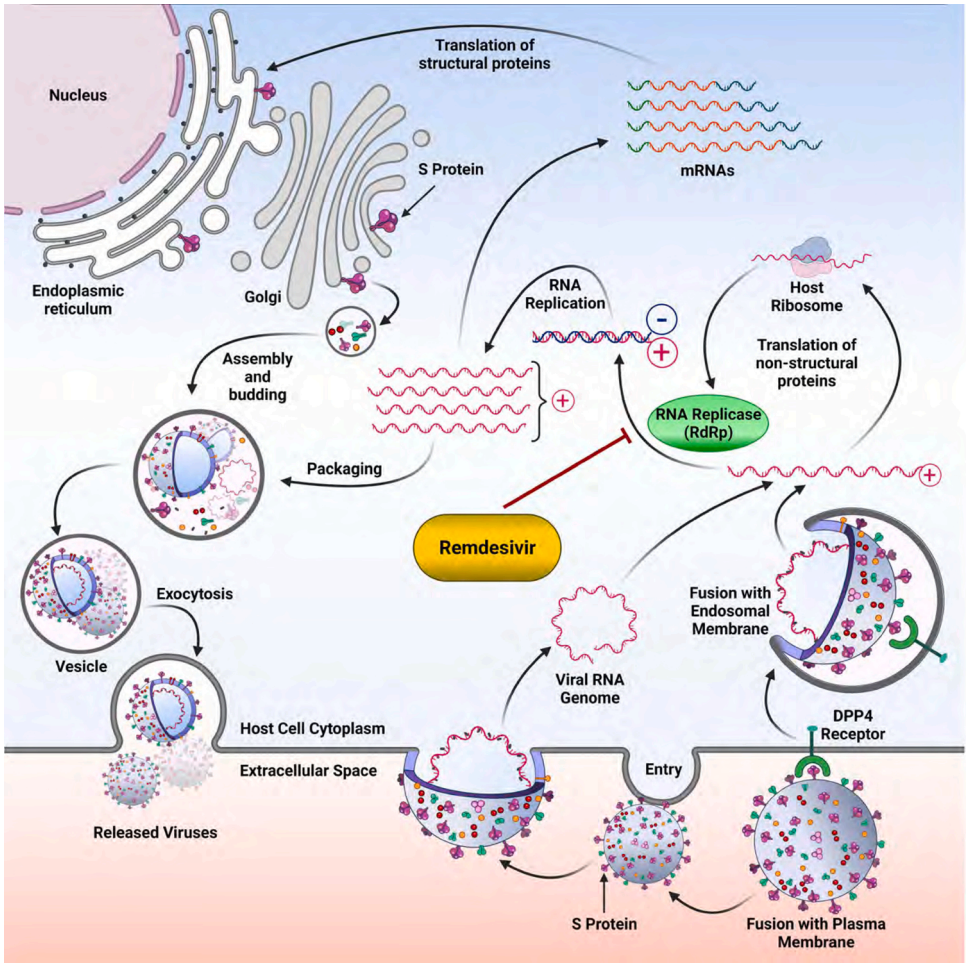

Fig. 4. The viral cycle of SARS-CoV-2 and the Remdesivir target. Remdesivir is an inhibitor of the RNA-replicase (RdRp), therefore inhibition of this enzyme impairs the replication of the viral genome and hence, blocks the life cycle of the whole virus, or renders it defective.

were hospitalized, required supplemental oxygen or died within 28 days of treatment compared with 11.1 % of patients on placebo (48 out of 434) (Kreuzberger et al., 2021).

3.5.4. Anakinra

Anakinra (Kineret) inhibits the biological activity of interleukin 1. It counteracts the production of NO, PGE2 and collagenase in the synovium, fibroblasts and chondrocytes. A systematic review and patient-level meta-analysis performed by Kyriazopoulou et al. examined pooled data for 1185 patients from nine studies, as well as individual patient data for 895 patients from six of the analyzed studies (Kyriazopoulou et al., 2021). Eight trials were observational studies, and one was a randomized controlled trial. The data taken into account were age, comorbidities, baseline partial pressure of oxygen in arterial blood, the ratio of arterial partial pressure of oxygen divided by inspired fraction of oxygen (PaO2/FiO2), C-reactive protein and lymphopenia. The mortality was significantly lower in patients treated with anakinra (38 [11 %] out of 342 patients) as compared with subjects receiving standard care with or without placebo (137 [25 %] out of 553; adjusted odds ratio [OR] 0.32 [95 % CI 0.20−0.51]). The mortality benefit was comparable between all subgroups, regardless of existing comorbidities, levels of ferritin l, or baseline PaO2/FiO2. Anakinra was more effective in reducing mortality in patients with a C-reactive protein concentration exceeding 100 mg/l (OR 0.28 [95 % CI 0.17−0.47]). Anakinra showed significant improvement in survival when administered without dexamethasone (OR 0.23 [95 % CI 0.12−0.43]), but not with additional dexamethasone (0.72 [95 % CI 0.37–1.41]). The use of anakinra, as compared to standard of care was not associated with a significantly increased risk of secondary infections (OR 1.35 [95 % CI 0.59–3.10]) (Kyriazopoulou et al., 2021).

3.5.5. Sotrovimab

Sotrovimab (Xevudy, also known as VIR-7831 and GSK4182136) is a monoclonal antibody with an activity against COVID-19. Sotrovimab was designed to attach to S protein of SARS-CoV-2. When it binds to S protein, the ability of the virus to enter the cells of the body are reduced. This is expected to reduce both the severity of the disease and need for hospitalization in COVID-19 (Sotrovimab, 2021). One article reported that the drug was administered at a dose of 500 mg or placebo. The primary efficacy outcome was hospitalization exceeding 24 h for any cause or death within 29 days of randomization. In this pre-specified interim analysis, which included an intention-to-treat population of 583 patients (291 in the sotrovimab group and 292 in the placebo group), 3 patients (1%) in the sotrovimab group, as compared with 21 patients (7%) in the placebo group, experienced disease progression leading to hospitalization or death (relative risk reduction, 85 %; 97.24 % confidence interval, 44–96; $p = 0.002$). In the placebo group, 5 patients were admitted to the ICU, including 1 who died by day 29. The safety assessment was performed in 868 patients (430 in the sotrovimab group and 438 in the placebo group). The adverse events were reported in 17 % of subjects in the sotrovimab group and 19 % of those in the placebo group; serious adverse events were less common with sotrovimab than with placebo (in 2% and 6% of the patients, respectively) (Gupta et al., 2021).

3.5.6. Tixagevimab and cilgavimab

Tixagevimab and cilgavimab (Evusheld), two monoclonal antibodies have been designed to attach to the spike protein of SARS-CoV-2 at two different sites. By attaching to the spike protein, the medicine is expected to stop the virus from entering the body's cells and causing infection. Because the antibodies attach to different parts of the protein, using them in a combination may be more effective than using either of them alone. The results of a recent trial funded by Astra Zeneca met the primary endpoint, with a dose of 600 mg of AZD7442 given by intramuscular (IM) injection reducing the risk of developing severe COVID-19 or death (from any cause) by 50 % compared to placebo in outpatients who had been symptomatic for seven days or less. The trial recorded 18 events in the AZD7442 arm (18/407) and 37 in the placebo arm (37/415). The LAAB was generally well tolerated in the trial. In a pre-specified analysis of participants who received treatment within five days of symptom onset, AZD7442 reduced the risk of developing severe COVID-19 or death (from any cause) by 67 % compared to placebo, with nine events in the AZD7442 arm (9/253) and 27 in the placebo arm (27/251) (AstraZeneca, 2021).

4. Other agents tested for potential efficacy in treating COVID-19 infection

4.1. Hydroxychloroquine

During the early days of the COVID-19 pandemic, many scientists and physicians placed hope in hydroxychloroquine (HCQ) and other antimalarial drugs. Moreover, non-randomized studies describing the positive effects of this drug are cited more often than any subsequent randomized trials about its lack of clinical benefit or even harmful side-effects (Bellos, 2021). With time, the severity of adverse effects and long-term consequences of HCQ treatment were elucidated (Drożdżal et al., 2020; Diaz-arocutipa and Hernandez, 2021). HCQ used both in monotherapy and in combination with azithromycin has been shown to increase the prevalence of a prolonged QTc as a side effect. An association with higher incidence of arrhythmias has not been demonstrated, although this is possibly due to underestimated reporting frequency72].

According to studies with a high level of certainty surrounding their evidence, HCQ does not reduce mortality in patients with COVID-19 (Self et al., 2020; Kashour et al., 2021). Moreover, a meta-analysis performed by Axfors et al., showed that patients had an all-cause combined mortality OR of 1.11 for hydroxychloroquine (95 % CI: 1.02–1.20) (Axfors et al., 2021). The effect of pharmacological prophylaxis in COVID-19 has also been disputed. Bartoszko et al., showed that taking HCQ has practically no effect on hospital admission or mortality, but it significantly increased the incidence of side effects. A meta-analysis of the available RCTs demonstrated no positive effects of the drug, but instead the incidence of side effects increased [RR = 1.81 (95 % CI: 1.36–2.42); $p < 0.05$] (Bartoszko et al., 2021). The study authors, do not recommend the use of chloroquine and hydroxychloroquine for either post-exposure prophylaxis or the treatment of COVID-19.

4.2. Colchicine

Colchicine may play a role in reducing the symptoms of COVID-19, as it binds to b-tubulin hence blocking microtubule polymerization. This in turn affects the spindle, and therefore reduces the movement and degranulation of intracellular lysosomes and the release of lysozymes, chemoattractants, and lactic acid. It inhibits the phagocytosis of sodium urate crystals by leukocytes, and reduces the breakdown of leukocyte cell membranes through their mobilization, migration, and the ability to adhere (Leung et al., 2015). It is characterized by anti-inflammatory effects achieved through a reduction of leukocyte migration, inhibition of endothelial adhesion, reduction in interleukin production, and cytokine storm prevention (Vitiello and Ferrara, 2021). Colchicine is a powerful anti-inflammatory agent routinely used to treat gout, viral pericarditis, coronary artery disease, and familial Mediterranean fever. Golpour et al., in a meta-analysis analyzed the effect of colchicine on the treatment of COVID-19. Colchicine was shown to be responsible for reducing mortality and length of hospitalization, and may therefore be an effective therapeutic option to improve COVID-19 treatment (Golpour et al., 2021).

4.3. Convalescent plasma

The concept of using convalescent plasma in the treatment of COVID-19 was enthusiastically received by clinicians, internationally. The premise was based on the theory that antibodies produced by convalescent patients would help the recipients' body combat the infection and improve their prognosis. The initial results were very promising, but the intervention group not only included COVID-19 patients, but also those with SARS, MERS, and influenza (Aviani et al., 2021). In a meta-analysis of COVID-19 patients, Bansal et al., showed that adding convalescent plasma to the standard of care reduced mortality among patients (Bansal et al., 2021a). A second meta-analysis by Janiaud et al., did not demonstrate the beneficial effect of administering convalescent plasma to patients (Janiaud et al., 2021). Furthermore, Prasad et al., considered the most recent data in both randomized clinical trials and cohort studies, suggesting a possible weak association, although underlined the need for further randomized trials (Prasad et al., 2021). Finally, Korley et al., published the results of a recent trial investigating the effect of convalescent plasma on the progression of COVID-19 in high-risk patients (n = 511). This study showed no effect on disease progression and length of hospitalization (Korley et al., 2021). The study authors do not recommend the routine use of convalescent plasma in patients hospitalized with COVID-19.

4.4. Amantadine

Amantadine hydrochloride, a synthetic tricyclic amine, is an antiviral drug known since the 1960s for the treatment of influenza A. It works by blocking M2 ion channels, inhibiting viral entry into cells, and inhibiting viral replication (Raupp-Barcaro et al., 2018a).

A model was proposed by Abreu et al., in which amantadine blocks viroportin E of the SARS-CoV-2 virus, preventing the release of genetic material into the host nucleus (Aranda-Abreu et al., 2020). It was also shown to inhibit the replication of the virus *in vitro*, however, this occurred only at a concentration higher than that achievable with oral supplementation (Fink et al., 2021).

When discussing amantadine, it is worth mentioning the neurological complications of COVID-19, i.e. agitation, myoclonus, abulia, alogy (Baller et al., 2020), brain fog, and chronic fatigue (Graham et al., 2021). Studies are emerging to assess the effects of amantadine on alleviating theses neurological symptoms. It has been suggested that amantadine can potentially help in the treatment of catatonia, especially in patients with contraindications to benzodiazepines due to respiratory failure (Raupp-Barcaro et al., 2018b). Additionally, amantadine may support the treatment of depressive disorders (Zaidi and Dehgani-Mobaraki, 2021). The study authors did not recommend the routine use of amantadine in COVID-19 patients limiting its use to a clinical trial.

4.5. Ivermectin

Ivermectin is one of the most commonly used drugs to treat parasitic infections in humans as well as in animals in veterinary medicine. Its mechanism is based on the selective, positive allosteric modulation of glutamate chloride channels found in nematodes and insects. It acts by binding to these channels, leading to an influx of chloride ions, causing cell hyperpolarization and thus dysfunction. Moreover, at higher concentrations, ivermectin can also bind to GABA receptors (Zaidi and Dehgani-Mobaraki, 2021). Ivermectin is rapidly absorbed orally and has high liposome solubility. Moreover, it is metabolized in the liver (by the

cytochrome P450 system) and almost exclusively excreted in feces (González Canga et al., 2008). One of the main potential mechanisms of ivermectin action is based on binding to the importin α (IMPα)/β1 heterodimer complex. IMPα/β1 participates in binding to the CoV load protein in the cytoplasm and transports it through the nuclear pore complex (NPC) into the nucleus, where it breaks down and the viral load assists in reducing the host cell's antiviral response, thereby increasing the infection. Ivermectin binds to the IMPα/β1 and destabilizes it, thus preventing it from binding the viral protein and entering the nucleus. This likely results in decreased inhibition of the immune response, leading to a normal, more effective antiviral reaction (Wagstaff et al., 2012).

Ivermectin has been examined in several studies, including that by Zein et al., who performed a review of the meta-analyses and meta-regression of randomized controlled trials. Among the available trials, they searched for the effectiveness of ivermectin in SARS-CoV-2 virus infections as compared to control patients with standard of care or a placebo. The primary endpoint that was evaluated was mortality. In total, 9 RCTs involving 1788 patients were analyzed in this meta-analysis, revealing that ivermectin was associated with a reduction in mortality [RR = 0.39 (95 % CI: 0.20 – 0.74); p = 0.004]. However, the benefit of ivermectin and this reduced mortality were impeded by hypertension [RR = 1.08 (95 % CI: 1.03–1.13); p = 0.001]. A sensitivity analysis using the fixed effects model showed that ivermectin reduced all-cause mortality [RR = 0.43 (95 % CI: 0.29 – 0.62); $p < 0.001$] and the severe COVID-19 subgroup [RR = 0.48 (95 % CI: 0.32–0.72); $p < 0.001$] (AFMZ et al., 2021).

However, other studies did not report statistically significant differences in mortality (Ravikirti and Pattadar, 2021), length of hospitalization (Abdulamir et al., 2021a) and clinical endpoints, disease progression, recovery, the occurrence of symptoms (Okumuş et al., 2021). The study authors did not recommend the routine use of ivermectin in COVID-19 patients, limiting its use to a clinical trial.

4.6. Niclosamide

Niclosamide (NIC) is an oral chlorinated salicylanilide. In clinical practice, it is a drug used to treat tapeworm infections. Its mechanism of action is centered around decoupling the electron transport chain from ATP synthase, thereby abolishing ATP synthesis. When administered orally, NIC specifically induced the degradation of the androgen receptor variant V7 (AR-V7) via a proteasome-mediated pathway. This action decreased the expression of the AR variant, inhibiting its transcriptional activity and reducing the recruitment of AR-V7 into the prostate-specific antigen (PSA) gene promoter. NIC also prevented AR-V7-mediated phosphorylation and activation of STAT3 (Kadri et al., 2018). In addition, there are reports of the antiviral activity of NIC against the influenza virus and HRV (Jurgeit et al., 2012). Various drug repurposing screens identified NIC as a potential drug candidate against COVID-19. Prevention of viral entry by altering endosomal pH and prevention of viral replication by inhibition of autophagy are the plausible mechanisms of action of NIC against COVID-19. Therefore, the clinical efficacy of NIC against COVID-19 therefore needs to be further evaluated (Pindiprolu and Pindiprolu, 2020).

One study in an animal model assessed the efficacy of NIC-Lysozyme (NIC-hLYS) particles against the SARS-CoV-2 infection. A once-daily administration in the form of nasal NIC-hLYS particles suspended in 0.45 % NaCl resulted in a 30 % survival rate in fatal SARS-CoV-2 infection. Moreover, it caused a statistically significant decrease in viral load in the lung after 10 days of treatment. By day 6 of treatment with 240 μg/kg NIC, interstitial pneumonia was significantly reduced and further resolved by day 14 (Brunaugh et al., 2020).

A randomized trial by Abdulamir et al., investigated the efficacy and safety of NIC as an adjunct to the standard of care in COVID-19 infection. This study was a randomized, controlled, open-label clinical study including 75 COVID-19 patients treated with standard of care plus NIC and 75 COVID-19 patients treated only with standard care therapy. Each group consisted of 25 mild, 25 moderate, and 25 severe COVID-19 patients. The main endpoints of the analysis were survival rate, time to recovery, and adverse reactions. NIC did not increase the survival rate as three severe COVID-19 patients in the NIC and control groups died ($p > 0.05$). However, when compared to the control group, NIC reduced recovery time in patients with moderate and severe COVID-19 by 5 and 3 days, respectively, but not in mild patients ($p \leq 0.05$). Interestingly, NIC reduced recovery time to five days in patients with comorbidities ($P \leq 0.05$), while shortening it by only one day in patients without comorbidities ($p > 0.05$). The authors concluded that NIC speeds up recovery by approximately 3–5 days in patients with moderate to severe COVID-19, especially those with underlying medical conditions. Hence NIC achieved clinical benefits by freeing up hospital beds for more patients in a pandemic crisis (Abdulamir et al., 2021b). The authors did not recommend the routine use of NIC in COVID-19 patients, limiting its use to a clinical trial.

4.7. Sarilumab

Sarilumab (Kevzara) is a human monoclonal antibody that acts to inhibit the binding of IL-6 to its α receptor. This drug is approved for the treatment of adults with moderately to severely active rheumatoid arthritis. Due to sarilumab ability to inhibit both soluble and membrane-bound IL-6 receptor, it has the potential to exert a therapeutic effect in patients with SARS-CoV-2 infection (KEVZARA (Sarilumab), 2017).

A study by Lescure et al., describes the effects of sarilumab in patients admitted to the hospital with severe or critical COVID-19. This was a phase 3 randomized, double-blind, placebo-controlled study on 416 patients allocated to 3 groups. Group one received a placebo, the second group received sarilumab at a dose of 200 mg and the third group received the drug at a dose of 400 mg. The authors concluded that the use of sarilumab was not effective in patients admitted to the hospital with COVID-19 and receiving oxygen supplementation. In patients with critical illness due to COVID-19, appropriately enhanced trials of targeted immunomodulatory therapies assessing survival as a primary endpoint, are suggested (Lescure et al., 2021a).

4.8. Chinese herbal medicine

In many environments, folk medicine plays an important role in the treatment of various diseases, especially those that people fear, or when conventional medicine is powerless or unable to propose effective treatment. This can be seen during the course of some cancers, and the beginning of the COVID-19 pandemic. Patients' questions often relate to Chinese herbal medicine (CHM) as a popular representative of alternative medicine. Currently, protocols of systematic reviews and meta-analyses for 7 preparations have been announced: Shufeng Jiedu (Wang et al., 2020a), Xuanfei Baidu (Zhao et al., 2021), Maxingshigan Decoction (Shao et al., 2020), Reyanning mixture (Li et al., 2021), Xiaoqinglong decoction (Ren et al., 2020), Lianhua Qingwen (Liu et al., 2020a), and Xiyanping (Zhou et al., 2020). As the authors suggest, these drugs have been used to treat COVID-19 in China, so scientific evidence is needed to evaluate their effectiveness. The study authors did not recommend the use of CHM in COVID-19 patients.

4.9. Dietary supplements

Vitamin C has been used as a remedy for cold-like symptoms for years. Studies on animal models show that vitamin C reduces vascular permeability, improves blood circulation, and due to its antioxidant effect, reduces the amount of free radicals (Armour et al., 2001; Chakrabarty et al., 1992). Furthermore, there have been reports of vitamin C used in combination with hydrocortisone and thiamine to treat sepsis and acute respiratory distress syndrome, significantly reducing mortality (Marik et al., 2017).

Gao et al., conducted a study in which vitamin C was administered at high doses to patients with COVID-19 (n = 46) and compared them with standard treatment (n = 30). The study showed a significant reduction in mortality and a lower need for respiratory support. Given the availability of vitamin C, there is a lack of large adequately powered studies confirming or contradicting the effectiveness of this supplement in treating COVID-19 (Gao et al., 2021). Huang et al., have published a protocol for a systematic review and meta-analysis of high-dose intravenous vitamin C administration, but have not released the results as of November 2021 (Huang et al., 2021).

Vitamin D supplementation during viral infections is also very popular. Vitamin D possess an immunomodulatory effect by altering the expression and secretion of proinflammatory cytokines (e.g. Il-6, TNF), interferon, and chemokines (Greiller and Martineau, 2015). A meta-analysis published by Rawat et al., examining the use of vitamin D in patients with COVID-19 demonstrated no significant reduction in mortality, ICU admission, or the need for invasive ventilation in patients receiving vitamin D supplementation (Rawat et al., 2021).

It is also worth mentioning that zinc, one of the micronutrients, was postulated to be effective in the combat against COVID-19. It was shown that supplementation with zinc reduced mortality in pneumonia without increasing the risk of therapy failure (Wang and Song, 2018). Its role is to reduce oxidative stress and inflammation (Prasad, 2014), thereby potentially alleviating the symptoms of COVID-19. Szarpak et al., performed a meta-analysis of the effect of zinc supplementation in COVID-19, although no statistically significant difference was found on mortality between patients using supplementation and those that were not (Szarpak et al., 2021). An overview on the COVID-19 drug effectiveness is presented in Tables 5 and 6.

5. Adjuvants/supportive treatment

5.1. Steroids

5.1.1. Dexamethasone

Dexamethasone is a synthetic glucocorticoid, a fluorinated derivative of prednisone that possesses a strong and long-lasting anti-inflammatory and immunosuppressive effect. The mechanism of action is based on the reduction of accumulated leukocytes and their adhesion to the endothelium. Moreover, dexamethasone inhibits phagocytosis and lysosomal breakdown, reduces the number of lymphocytes, eosinophils, monocytes, and blocks IgE-dependent secretion of histamine and leukotrienes. Finally, it inhibits the synthesis and release of cytokines, including interferon γ, TNF-α, GM-CSF, and interleukins IL-1, IL-2, IL-3, and IL-6. By inhibiting the activity of phospholipase A2 through lipocortin, it prevents the release of arachidonic acid, therefore reducing mediators of inflammation such as leukotrienes and prostaglandins (Ahmed and Hassan, 2020; Sinner, 2019).

Table 5
A summary of COVID-19 drug effectiveness meta-analyses.

Drug	No. patients	Outcome	Effect
Vitamin D (Rawat et al., 2021)	467	Mortality reduction	No effect; R = 0.55 (95 % CI 0.22–1.39), p = 0.21
HCQ (Amani et al., 2021)	6059	Mortality reduction	No effect, RR = 0.7 (95 % CI: 0.24–1.99)
HCQ (Bartoszko et al., 2021)	8161	Side effects	RR = 1.81 (95 % CI: 1.36–2.42), p < 0.05
HCQ (Axfors et al., 2021)	10,012	Increase of mortality	OR = 1.11 (95 % CI: 1.02–1.20)
Convalescent plasma (Bansal et al., 2021b)	27,706	Mortality reduction	OR 0.76 (95 % CI: 0.53–1.08), p = 0.13
Sarilumab (Lescure et al., 2021b)	416	Positive effect	HR = 1.03 (95 % CI 0.75–1.40]; p = 0.96

Legend: HCQ – hydroxychloroquine; HR – hazard ratio; OR – odds ratio; RR – risk ratio; 95 % Cl – 95 % confidence interval.

In one of the most comprehensive trials, patients were randomized to receive 6 mg oral or intravenous dexamethasone once daily for up to 10 days or to a control group that received the standard of care. The primary endpoint was mortality at 28 days. A total of 2104 patients were assigned to receive dexamethasone and 4321 received standard of care. Overall, 482 patients (22.9 %) in the dexamethasone group and 1110 patients (25.7 %) in the standard of care group died within 28 days after randomization [age-adjusted rate ratio = 0.83 (95 % confidence interval [CI]: 0.75–0.93); p < 0.001]. In the dexamethasone group, the death rate was lower than in the standard care group receiving invasive mechanical ventilation [29.3 % vs. 41.4 %; rate ratio = 0.64 (95 % CI: 0.51–0.81)] and receiving oxygen without invasive mechanical ventilation [23.3 % vs. 26.2 %; rate ratio = 0.82 (95 % CI: 0.72–0.94)], but not among those who did not receive respiratory support at the time of randomization [17.8 % vs. 14.0 %; rate ratio = 1.19 (95 % CI: 0.92–1.55)]. This study showed that dexamethasone treatment resulted in a lower 28-day mortality in patients hospitalized for COVID-19 who were undergoing mechanical ventilation or oxygen therapy, but not for those patients who did not receive respiratory support (Lim et al., 2021).

The results of the most recent trial pertaining the use of dexamethasone, the COVID STEROID 2 Trial provided by Munch et al. in October 2021 have shown that in COVID-19 patients with severe hypoxemia, the use of 12 mg/d of dexamethasone as compared with 6 mg/d of dexamethasone did not reduce 28-day survival without life support (Munch et al., 2021). In the 12 mg dexamethasone group the mortality at 28 days was lower (27.1 %) and in the 6 mg dexamethasone group was higher (32.3 %) (adjusted relative risk, 0.86 [99 % CI, 0.68–1.08]). Similarly, the death rate at 90 days was lower (32.0 %) in the 12 mg dexamethasone group as compared to mortality in the 6 mg dexamethasone group (37.7 %), with adjusted relative risk of 0.87 [99 % CI, 0.70–1.07]). Although the results of the by Munch et al. are supportive, but not definitive of improved outcomes when using 12 mg/d of dexamethasone, the study was underpowered. Therefore, the results of COVID STEROID 2 Trial do not satisfy the usual criteria to support change in practice, but further trials are needed to define the optimal dose of dexamethasone with definite survival benefit. The results of three on-going trials (NCT04381936, NCT04726098, NCT04663555) are highly awaited. Hence, the study authors recommended the use of dexamethasone in the routine care of patients with COVID-19, especially during hospitalization, but the optimal dose is yet to be established.

5.1.2. Budesonide

Another member of the glucocorticoid family which has recently been used to treat SARS-CoV-2 infections is budesonide. A randomized, phase 2 trial of inhaled budesonide versus standard of care (Steroids in COVID-19; STOIC study) was conducted in adults within 7 days of onset of mild COVID-19 symptoms. The dry powder of budesonide was administered via a turbine inhaler at a dose of 400 μg. Participants were asked to perform two inhalations twice a day. The primary endpoint was a COVID-19 related emergency department visit. Secondary endpoints were patient-reported symptom relief, body temperature, blood oxygen saturation, and SARS-CoV-2 virus load. For the pre-protocol population (n = 139), the primary endpoint was met in 10 (14 %) of 70 participants receiving the standard of care and 1 (1%) of 69 participants receiving budesonide [difference = 0.131 (95 % CI: 0.043 – 0.218); p = 0.004]. In the intention-to-treat population, the primary endpoint occurred in 11 (15 %) participants in the usual care group and two (3%) participants in the budesonide group [difference = 0.123 (95 % CI: 0.033 – 0.213); p = 0.009]. The number needed to treat with inhaled budesonide to reduce the worsening of COVID-19 was 8. Budesonide was also found to be safe, and only five (7%) participants reported self-limiting adverse events (Ramakrishnan et al., 2021). The study authors recommend the inhalation of steroids in the routine use in patients with COVID-19 in the early stages of the disease.

Table 6
Effectiveness of therapeutic agents in COVID-19.

Drug	No. patients	Dose	Outcome	Effect
Ivermectin (AFMZ et al., 2021)	1788	140 - 400 μg/kg	Mortality reduction	RR = 0.39 (95 % CI: 0.20–0.74); p = 0.004
Colchicine (Golpour et al., 2021)	5901	NA	Mortality reduction	RR = 0.644 (95 % CI: 0.555 – 0.748)
Niclosamide (Abdulamir et al., 2021a)	150	3 g per day	Reduced recovery time	$p \leq 0.05$
Tofacitinib (Gunay et al., 2021)	289	10 mg twice a day	Mortality reduction	HR = 0.49 (95 % CI: 0.15–1.63)
Bamlanivimab - Etesevimab (Dougan et al., 2021)	1035	2.8 g + 2.8 g	Hospitalizations or death	absolute risk difference = −4.8%; (95% CI − 7.4 - −2.3); RR = 0.3; $p < 0.001$
Bamlanivimab - Etesevimab (Gottlieb et al., 2021)	577	2.8 g + 2.8 g	Viral load	Viral load change = - 0.57 (95 % CI: −1.00 to −0.14); p = 0.01
Anticoagulants (Parisi et al., 2021)	25,719	therapeutic and prophylactic dose	Mortality reduction	RR = 0.50 (95 % CI: 0.40–0.62)
ASA (RECOVERY Collaborative Group, 2021)	14,892	150 mg	Mortality reduction	RR = 0.96 (95 % CI 0.89–1.04); p = 0.35
Dexamethasone (Lim et al., 2021)	6425	6 mg	Mortality reduction	RR = 0.83; (95 % CI: 0.75–0.93); $p < 0.001$
Budesonide (Ramakrishnan et al., 2021)	139	400 μg	Emergency visit/ hospitalization	RR = 0.131 (95 % CI: 0.043–0.218); p = 0.004

Legend: ASA – acetylsalicylic acid, aspirin, HR – hazard ratio; RR – risk ratio; 95 % Cl – 95 % confidence interval.

5.2. Anticoagulants

Heparin possesses potent anticoagulant activity, induced by catalyzing the thrombin-antithrombin reaction. In addition, heparin exerts an anti-inflammatory effect that may improve endothelial function, which may be beneficial for patients with COVID-19. To date, there are two studies comparing the low-molecular-weight (LMW) to unfractionated heparin, and both demonstrated a reduced risk of death with LMW compared with unfractionated heparin (Kirkup et al., 2021; Pawlowski et al., 2021). In one study, mortality for the primary population was 270/1939 *vs.* 390/1012 with an OR = 0.258 (95 % CI: 0.215–0.309); in-hospital mortality for the matched populations was 154/711 (22 %) *vs.* 268/733 (37 %) with an OR = 0.480 (95 % CI: 0.380–0.606) and 28-day mortality for matched populations 12/528 (2.3 %) *vs.* 44/463 (9.5 %) with an OR = 0.221 (95 % CI: 0.115 – 0.425). In addition, the addition of LMW heparin reduced hospitalization (10.99 days vs. 13.33 days; p = 0.005), and ICU admission (10.7 *vs.* 12.16; p = 0.00008), and finally reduced the number of patients transferred to the ICU [primary populations: 988/1936 vs. 717/1009, OR = 0.424 (95 % CI: 0.361 – 0.499); comparison of matched populations: 399/714 (56 %) vs. 481/732 (66 %), OR = 0.661 (95 % CI: 0.534 – 0.817)] (Kirkup et al., 2021).

In the second study, Pawlowski et al., showed that all-cause mortality for primary populations was reduced [11 (2.5 %) *vs.* 28 (17 %), RR = 6.76 (95 % CI: 3.39–12.7)], with the 28-day mortality for the primary populations of 9/244 (3.7) *vs.* 20/118 (17) (RR = 4.60, 95 % CI: 2.13–9.29)]. Additionally, end-points in favor of LMW heparin were reached in terms of patients transferred to the ICU primary population (88 (20 %) *vs.* 50 (30 %) RR = 1.51 (95 % CI: 1.12–2.03) (Pawlowski et al., 2021). The study authors recommended the routine use of anticoagulants in patients with COVID-19, especially during hospitalization.

5.3. Acetylsalicylic acid

Acetylsalicylic acid (ASA, aspirin) belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs) that possess anti-inflammatory, antipyretic, and analgesic properties. Its mechanism of action is based mainly upon inhibiting cyclooxygenases (COX) in two distinct ways. Constitutive COX (COX-1) is responsible for the synthesis of prostaglandins that fulfill physiological functions. On the other hand, inducible COX (COX-2) is responsible for the synthesis of pro-inflammatory prostaglandins at the site of inflammation. ASA mainly inhibits COX-1, and to a lesser extent, COX-2. By irreversibly inhibiting platelet COX-1 and crippling thrombogenesis, it exerts an anti-aggregating effect. At higher doses, it acts as an antithrombotic agent by antagonizing vitamin K (Tanasescu et al., 2000). Moreover, the pleiotropic effects of ASA include the modulation of endothelial function (Sayed Ahmed et al., 2021), and therefore it may have a role in preventing COVID-19 complications (Dzeshka et al., 2016). Moreover, ASA has been shown to carry antiviral activity against RNA viruses in the respiratory tract, such as influenza A virus and human rhinoviruses, but its mode of action is still unknown and requires further research (Glatthaar-Saalmüller et al., 2017).

In the RECOVERY study, Horby et al., described the effectiveness of ASA in COVID-19 infection. In this randomized, controlled, open-label platform study, several possible treatments were compared with standard of care in patients hospitalized for COVID-19. Eligible and consenting adults were randomly assigned in a 1:1 ratio to either standard care (7541 patients) or standard care plus 150 mg of ASA (7351 patients) once a day until discharge from the hospital. The primary endpoint was mortality at 28 days. This study demonstrated that 1222 (17 %) patients assigned to ASA and 1299 (17 %) patients assigned to ordinary care died within 28 days (RR = 0.96; 95 % CI: 0.89–1.04; p = 0.35). Among subjects who did not require invasive mechanical ventilation at baseline, there was no significant difference in the proportion meeting the composite endpoint of invasive mechanical ventilation or death (21 % vs. 22 %; HR = 0.96; 95 % CI: 0.90–1.03; p = 0.23). The use of ASA was associated with an absolute reduction in the number of thrombotic events by 0.6 % and an absolute increase in the number of major bleeding events by 0.6 % (RECOVERY Collaborative Group, 2021). Furthermore, the study by Chow et al., reported promising effects of ASA in SARS-CoV-2 infection. Among the 412 patients included in the study, 314 did not receive ASA (76.3 %) while 98 patients (23.7 %) did. The significant differences were reported between the two groups in the ICU admission rate (51 % non-ASA *vs.* 38.8 % ASA; $p < 0.05$) and the rate of mechanical ventilation (48.4 % non-ASA vs. 35.7 % ASA; $p < 0.05$). After the adjustment of confounding variables, the ASA use was reported to decrease the risk of mechanical ventilation (HR = 0.56; 95 % CI: 0.37 – 0.85; p = 0.007), admission to intensive care unit (HR = 0.57; 95 % CI: 0.38–0.85; p = 0.005) and in-hospital death adjusted (HR = 0.53; 95 % CI: 0.31–0.90; p = 0.02) (Chow et al., 2021). Accordingly, the study authors suggested potential use of acetylsalicylic acid in patients with COVID-19, especially in clinical trials.

5.4. Statins

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors, are lipid-lowering drugs that display pleiotropic effects. As acute respiratory distress syndrome (ARDS), the main cause of death from COVID-19, is caused by exaggerated inflammatory response, the immunomodulatory properties of statins have become of interest in the context of COVID-19 research, and have previously shown a beneficial

effect in the treatment of autoimmune, inflammatory, and infectious diseases (Lima Martínez et al., 2020). These agents could potentially limit the cytokine storm by blocking NF-κB and NLRP3 inflammasomes (Rodrigues-Diez et al., 2020). Moreover, statins also affect the cell cycle, even leading to its arrest, induce autophagy and apoptosis, which is likely to further limit viral replication (Ahmadi et al., 2020). However, the significance of the mechanism in which statins possibly increase SARS-CoV-2 virus entry by inducing ACE-2 expression is still not fully known (Rodrigues-Diez et al., 2020; Zhang et al., 2020).

The wide-spread use of statins has enabled the researchers to conduct large-scale retrospective studies among COVID-19 patients. Members of our team performed such a study of statin-treated *vs* non-treated people, who were infected with SARS-CoV-2. However, data from a group of 150 patients, 75 of which received statins, failed to reach statistical significance. However, these data have encouraged us to conduct larger retrospective analyses or even prospective studies (Peymani et al., 2021). A large retrospective study on 13,981 patients from China found an association between the statin use and lower risk of mortality (Zhang et al., 2020).

A meta-analysis of 4 studies showed that the use of statins is associated with a significantly reduced hazard for fatal or severe disease (pooled HR = 0.70; 95 % CI: 0.53–0.94), although these results based on 8990 patients strongly highlight a need for prospective studies (Kow and Hasan, 2020).

The currently available data seems encouraging and suggests that in no case should the use of statins be abandoned during COVID-19 infection. However, it is too soon to include statins in the routine therapeutic plan for COVID-19 treatment (Subir et al., 2020). Moreover, people, who start therapy with statins due to cardiovascular diseases during the pandemic should be aware that some of the potential side effects might mimic COVID-19. Muscle-related symptoms especially, are similar when comparing the side-effects of statins or viral infection (Karalis DG, 2020).

6. Treatment of COVID-19 complications

COVID-19 symptoms can, in some cases, persist for months. The virus can damage the lungs, heart and brain, which significantly increases the risk of long-term health issues. This group of conditions has been called post−COVID-19 syndrome or long COVID-19 (Datta et al., 2020). In general, they are considered to be the effects of COVID-19 that persist for more than four weeks after diagnosis (Silva Andrade et al., 2021). SARS-CoV-2 can cause severe inflammation that is triggered by the immune system, which responds by increasing the rate of coagulation, which is triggered largely due to other systems in the body being affected by blood clots, such as the lungs, kidneys, liver, or heart. Moreover, COVID-19 can also weaken blood vessels and cause them to leak, which further contributes to the potential long-term complications affecting the kidneys and liver (Jin et al., 2020). The SARS-CoV-2 infection requires the cooperation of several essential systems to maintain homeostasis. The direct effect of SARS-CoV-2 hyperinflammation induces the production of endogenous compounds that promote the alteration of vascular hemostasis (Liu et al., 2020b). Furthermore, the release of pro-inflammatory and pro-thrombotic cytokines has a direct effect on blood coagulation. These factors result in disseminated intravascular coagulation and the formation of thromboembolic conditions that can affect various tissues, especially those which are more sensitive to ischemic processes, such as pulmonary, cardiovascular, and cerebrovascular tissues (Jin et al., 2020; Giustino et al., 2020). The cardiopulmonary system especially is severely affected (Cobos-Siles et al., 2020). The lungs suffer from gradual functional failure, which is reflected by hypoxia and pathological findings (Silva Andrade et al., 2021; Al-Khawaga and Abdelalim, 2020). Among the most common pathologies of the lung, respiratory failure, pulmonary thromboembolism, pulmonary embolism, pneumonia, pulmonary vascular damage, and post-viral pulmonary fibrosis should be highlighted (Sakr et al., 2020; George et al., 2020; Lechowicz et al., 2020). So far, there is no single, proper guideline for treating pulmonary complications after COVID-19. It has been suggested that physical exercise and appropriate rehabilitation, including breathing exercises, may help to resolve pulmonary symptoms (Crook et al., 2021). In more severe cases, the use of opioids may reduce respiratory effort (Jennings, 2002). However, lung fibrosis may be a long-term complication. Due to the relatively short follow-up period from the first infection, the available data on this phenomenon is limited. Therefore, it is suggested that the treatment recommendations regarding idiopathic pulmonary fibrosis be followed.152] There have been reports in the literature that the use of spironolactone during COVID-19 infection can prevent fibrosis(Kotfis et al., 2021).

The most experienced cardiac complications include angina, acute coronary syndromes, and arrhythmias. The NICE recommendations point to the use of beta blockers in these cases (National Institute for Health and Care Excellence, 2021, 2020; National Institute for Health and Care Excellence, 2016). Furthermore, remission of one complication, myocarditis, might depend on immunomodulatory effect (Sinagra et al., 2016). Complications related to the nervous system following COVID-19 infection include loss of taste, smell and hearing, headaches, spasms, convulsions, confusion, visual disturbances, neuralgia, dizziness, disturbance of consciousness or delirium, nausea and vomiting, hemiplegia, ataxia, stroke, as well as cerebral hemorrhage (Favas et al., 2020; Samaranayake et al., 2020; Almufarrij et al., 2020; Kennedy et al., 2020; Kotfis et al., 2020; Pun et al., 2021). According to Crook et al., chronic fatigue syndrome can be compared to the myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) so treatment may include cognitive behavioral therapy (CBT) and graded exercise therapy (GET) (Crook et al., 2021). In the case of cognitive impairment, the so-called brain fog, apart from psychological support, methylphenidate, donepezil, modafinil, and memantine may also be helpful (Crook et al., 2021; Chemo brain, 2021; Theoharides et al., 2021).

COVID-19 infections can cause macro- and micro-thromboembolic renal dysfunction as well as trigger microvascular obstruction and infarction. Idilman *et al.,* found that a large number of patients with mild to moderate COVID-19 had perfusion deficits (PD) in their lungs and kidneys, which may be suggestive of the presence of systemic microangiopathy with microthrombosis (Acharya et al., 2020; Idilman et al., 2021). In addition to kidney damage, the other system affected by complications from COVID-19 infection is the digestive system and liver. A meta-analysis of thirty-one studies examining the incidence of gastrointestinal symptoms in 4682 patients found that diarrhea and anorexia were among the most significant gastrointestinal symptoms associated with COVID-19. In addition, it was observed that patients admitted to ICU or with high intensity were more likely to develop abdominal pain and increased hepatic inflammatory markers such as aspartate aminotransferase or alanine aminotransferase (Dong et al., 2021).

One of the other potential long-term complications of COVID-19, due to long-term persistence of viral particles in organs, is interaction with autophagy machinery (Habibzadeh et al., 2021). This interaction induces inhibition of autophagy flux, which potentially is involved in potentiation of cancer progression and metastasis and immune escape in COVID-19 survivors (Habibzadeh et al., 2021).

7. Summary

Prophylaxis with SARS-CoV-2 vaccines is the most effective modality to prevent and eliminate COVID-19. COVID-19 symptomatology varies between patients and treatment needs to be tailored towards specific symptoms, as there are many critical points of disease progression that can be targeted. The development and progression of COVID-19 can be viewed as a multi-stage process (Fig. 5) that begins with the exposure to the virus, followed by the SARS-CoV-2 infection phase, and then the initiation of COVID-19 disease processes such as early infection, pulmonary phase and inflammatory storm phase. Pharmacological

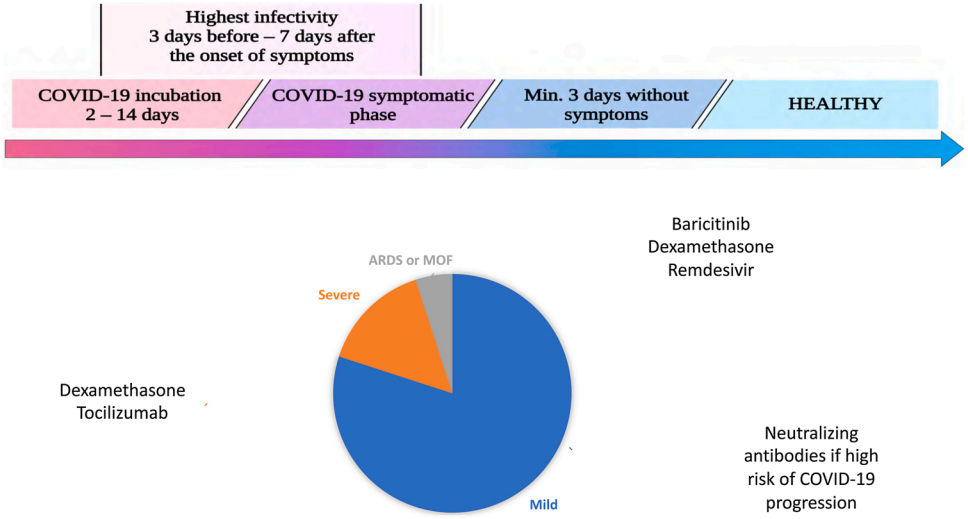

Fig. 5. Graphical representation of currently recommended therapeutic agents depending on the clinical condition. Top shows the natural course of COVID-19 infection. The symptomatic phase occurs after incubation at >20 % infection. Out of patients in critical condition even around 50 % die. Bottom shows suggested therapeutic interventions depending on the course of the disease 80 % – mild course of the disease; neutralizing antibodies recommended if high risk of disease progression. 15 % - severe course of the disease; dexamethasone and remdesivir recommended for patients with $SpO_2 \leq 94$ % on room air; if rapidly increasing oxygen need and systemic inflammation – consider baricitinib or tocilizumab. 5% - acute respiratory distress syndrome (ARDS) or multi-organ failure develops; use dexamethasone and consider tocilizumab.

interventions at any of these stages are required in order to minimize the effects. Moreover, the timing of the intervention is critical. Currently, behavioral modifications are necessary to prevent exposure to SARS-CoV-2, and public health guidelines for social distancing, masking, and hygiene are recommended. Rigorously tested pharmacological strategies to reduce and block SARS-CoV-2 virus infection and COVID-19 development are the subject of thousands of trials around the world to reduce and contain the global epidemic. In the latter respect, Pfizer Inc., recently announced that its investigational novel COVID-19 oral antiviral candidate, PAXLOVID™ (PF-07321332), significantly reduced hospitalization and death, based on an interim analysis of the phase 2/3 EPIC-HR (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19 in **H**igh-**R**isk Patients) randomized, double-blind study of non-hospitalized adult patients with COVID-19, who are at high risk of progressing to severe illness. The scheduled interim analysis demonstrated an 89 % reduction in risk of COVID-19-related hospitalization or death from any cause compared to placebo in patients treated within three days of symptom onset (primary endpoint); 0.8 % of patients who received PAXLOVID™ were hospitalized through Day 28 following randomization (3/389 hospitalized with no deaths), compared to 7.0 % of patients who received placebo and were hospitalized or died (27/385 hospitalized with 7 subsequent deaths). The statistical significance of these results was high ($p < 0.0001$). Similar reductions in COVID-19-related hospitalization or death were observed in patients treated within five days of symptom onset; 1.0 % of patients who received PAXLOVID™ were hospitalized through Day 28 following randomization (6/607 hospitalized, with no deaths), compared to 6.7 % of patients who received a placebo (41/612 hospitalized with 10 subsequent deaths), with high statistical significance ($p < 0.0001$). In the overall study population through Day 28, no deaths were reported in patients who received PAXLOVID™ as compared to 10 deaths (1.6 %) in patients who received placebo.

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