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Review Article

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COVID-19 Therapeutics: An Update on Effective Treatments Against Infection With SARS-CoV-2 Variants

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic is one of the most consequential global health crises in over a century. Since its discovery in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to mutate into different variants and sublineages, rendering previously potent treatments and vaccines ineffective. With significant strides in clinical and pharmaceutical research, different therapeutic strategies continue to be developed. The currently available treatments can be broadly classified based on their potential targets and molecular mechanisms. Antiviral agents function by disrupting different stages of SARS-CoV-2 infection, while immune-based treatments mainly act on the human inflammatory response responsible for disease severity. In this review, we discuss some of the current treatments for COVID-19, their mode of actions, and their efficacy against variants of concern. This review highlights the need to constantly evaluate COVID-19 treatment strategies to protect high risk populations and fill in the gaps left by vaccination.

Keywords: COVID-19; Severe acute respiratory syndrome coronavirus 2; Antiviral agents; Immunotherapy; Variants

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly contagious respiratory disease that affected more than 600 million people worldwide, with over 6.5 million deaths to date (1). It was declared a global pandemic on March 11, 2020 by the World Health Organization (WHO), marking the first ever pandemic caused by a coronavirus (2). Its causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belongs to the genus *Betacoronavirus* of the family *Coronaviridae* and is closely related to SARS-CoV (up to 79% nucleotide identity) that caused the 2002–2003 SARS epidemic and to Middle East respiratory syndrome coronavirus (MERS-CoV; up to 50% nucleotide identity) that has been causing sporadic outbreaks in the Arabian peninsula since 2012 (3,4). COVID-19 is one of the most consequential global health crises since the 1,918 influenza pandemic, resulting in dramatic loss of livelihood and human life worldwide. Although significant strides in clinical research are continuously made, limiting further spread of the virus through treatment and immunization remains a priority. In this review, we provide an update on the currently used treatments against COVID-19,

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
3CLpro, 3-chymotrypsin-like protease; ACE, angiotensin-converting enzyme; ACTT1, Adaptive Covid-19 Treatment Trial; AI, artificial intelligence; ARDS, acute respiratory distress syndrome; BAM, bamlanivimab; COVID-19, coronavirus disease 2019; CRS, cytokine release syndrome; DCV, daclatasvir; DEX, dexamethasone; ECMO, extracorporeal membrane oxygenation; EMA, European Medicines Agency; ETE, etesevimab; EUA, emergency use authorization; FDA, Food and Drug Administration; HCQ, hydroxychloroquine; HCV, hepatitis C virus; ICU, intensive care unit; mAb, monoclonal Ab; MERS-CoV, Middle East respiratory syndrome coronavirus; NAK, Numb-associated kinases; NHC, β-D-N4-hydroxycytidine; NHC-TP, β-D-N4-hydroxycytidine-5'-triphosphate; nsp, non-structural proteins; ORF, open reading frame; RBD, receptor binding domain; RCT, randomized controlled trial; RdRp, RNA-dependent RNA polymerase; RDV, remdesivir; RECOVERY, Randomised Evaluation of COVID-19 Therapy; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; S protein, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAVE-MORE, suPAR-guided Anakinra treatment for Validation of the risk and Early Management Of seveRE respiratory failure by COVID-19; SOC, standard of care; SOF, sofosbuvir; SOTr, solid organ transplant recipient; suPAR, soluble urokinase plasminogen activator receptor; TMPRSS2, transmembrane protease serine 2; TP, triphosphate; VEL, velpatasvir; VOC, variants of concern; WHO, World Health Organization.

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discuss their mode of actions, and examine the clinical trials done to evaluate the safety and efficacy of these treatments against the currently circulating SARS-CoV-2 sublineages.

Similar to other coronaviruses, SARS-CoV-2 is an enveloped, single-stranded, positive-sense RNA virus composed of 4 main structural proteins: spike, envelope, membrane, and nucleocapsid; 16 non-structural proteins (nsp); and 5–8 accessory proteins (5). The spike protein (S protein) plays a critical role in attachment, fusion, entry, and transmission of the virus. SARS-CoV-2 initiates entry with the cleavage of its S protein into S1 and S2 subunits. The receptor binding domain (RBD) of the S1 subunit then binds the host angiotensin-converting enzyme 2 (ACE2), while the S2 subunit anchors the S protein to the host membrane (**Fig. 1**) (6). ACE2 is a cell surface receptor broadly expressed in epithelial cells of the lungs and the small intestine, as well as in other organs such as the heart, kidney, and esophagus (6,7). Upon binding of the RBD to ACE2, both S protein subunits undergo dramatic conformational changes, exposing an additional site within the S2 subunit, termed the S2' site or the priming site (8). The cleavage of this site facilitates membrane fusion and

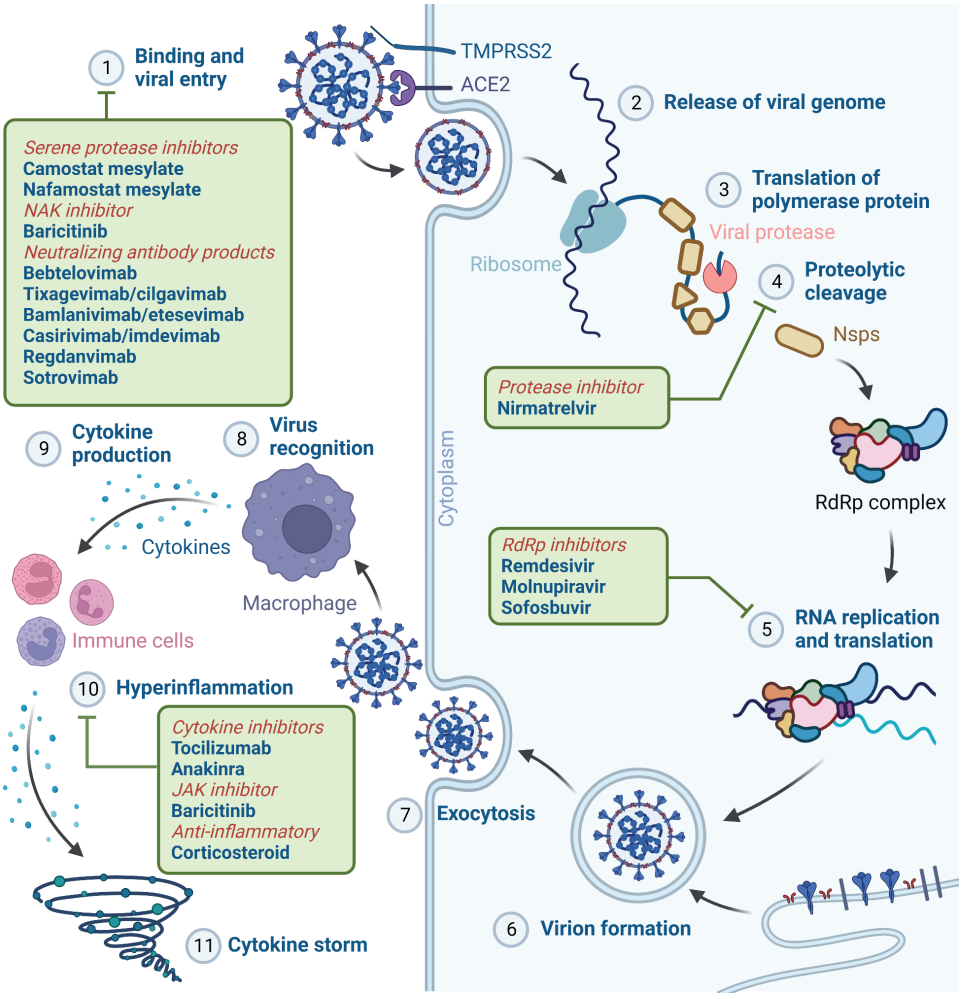

Figure 1. Targets of antiviral and immune-based therapies and their modes of action. Currently used treatments against SARS-CoV-2 infection can be divided into 1) direct-acting antivirals, which inhibit certain steps in the SARS-CoV-2 replication cycle; and 2) immune-based therapeutics, which modulate the immune response (cytokine and JAK inhibitors) or have direct immune effector functions (neutralizing antibodies).

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eventual release of the viral genome into the host cell cytoplasm (8). SARS-CoV-2 typically employs the transmembrane protease serine 2 (TMPRSS2) to cleave the S2' site (8). In the absence of TMPRSS2, the SARS-CoV-2–ACE2 complex enters the cell via clathrin-mediated endocytosis where the S2' site is instead cleaved by cathepsin L (8,9).

The release of SARS-CoV-2 RNA in the host cell cytoplasm marks the onset of viral gene expression (10). As in other coronaviruses, more than two-thirds of the SARS-CoV-2 genome capacity is occupied by 2 large open reading frames (ORF1a and ORF1b) that constitute the replicase gene (11). Translation of these ORFs produces 2 polyproteins, pp1a and pp1ab, that mediate all the functions required for infection (12). ORF1a-encoded proteases then initiate the proteolytic cleavage of pp1a and pp1ab to release 16 nsp: nsp1–11 from pp1a and nsp1–10, nsp12–16 from pp1ab, which are crucial to viral replication (10). Certain nsp, specifically, nsp5 or the 3-chymotrypsin-like protease (3CL-pro) and nsp12 or the viral RNA-dependent RNA polymerase (RdRp), are considered promising antiviral targets (13).

Most mutations in the SARS-CoV-2 genome have no apparent effects on the virus (14). However, some mutations may alter certain aspects of the SARS-CoV-2 biology (pathogenicity, infectivity, and transmissibility), giving rise to SARS-CoV-2 variants that are significantly different from the ancestral strains (15,16). Owing to the breadth and persistence of the spread of SARS-CoV-2 in the human population, several notable SARS-CoV-2 variants have emerged throughout the course of the pandemic. Based on the risk they pose to global public health, five variants of concern (VOC) were declared: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) variants (17). To date, the Omicron variant, including its sublineages (BA.1, BA.2, BA.3, BA.4, BA.5, and descendent lineages) is still circulating worldwide (17). The changes in biology of these variants may render the currently available vaccines and treatments against SARS-CoV-2 ineffective (18). It is therefore important to continuously examine the efficacy of the different COVID-19 treatments against these variants.

Currently available therapeutic options against COVID-19 can be broadly classified into antiviral agents and immune-based treatments. Antiviral agents are virus-specific treatments targeting different stages of SARS-CoV-2 life cycle, while immune-based treatments neutralize SARS-CoV-2 infection or modulate host inflammatory responses. Information about the efficacy of these treatments is mostly inconsistent, especially with the emergence of various SARS-CoV-2 variants and their sublineages. In this context, this review discusses several therapeutic options for COVID-19 based on their potential targets, molecular mechanisms, and efficacy against currently circulating VOCs.

ANTIVIRAL AGENTS

Remdesivir (RDV)

RDV (GS-5734, Veklury®; Gilead Sciences, Foster City, CA, USA) is a nucleotide analogue prodrug first developed in search of therapeutic agents against RNA viruses with pandemic potential (**Table 1**) (19). Its active form, RDV triphosphate, interacts with the viral RdRp which causes delayed chain termination during viral RNA replication (20). In multiple *in vitro* systems, RDV inhibited several coronaviruses (SARS-CoV, MERS-CoV, human CoV, and bat CoV), indicating broad-spectrum antiviral activity and potential utility against other coronaviruses that may emerge in the future (21).

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Table 1. Summary of clinical studies and approvals for COVID-19 antiviral treatments

Antiviral agents	Target	FDA/EMA approval	Findings
Remdesivir (RDV)	Viral RdRp	**FDA approval for treatment (October 2020)**: Patients requiring hospitalization (age: ≥12 years; weight: ≥40 kg) **EMA approval for treatment (July 2020)**: Patients with pneumonia requiring supplemental oxygen (age: ≥12 years; weight: ≥40 kg)	• RDV treatment prevented the development of a more severe disease, reduced disease burden, and decreased the need for health care resources (Phase 3, ACTT1, NCT04280705) (27) • No significant difference in efficacy between a 5-day and a 10-day course of RDV (Phase 3, NCT04292899) (28) • Patients in 5-day treatment group had significantly higher odds of having better clinical distribution (Phase 3, NCT04292730) (29) • RDV treatment produced no significant impact on patients who were already receiving ventilation, and had minimal effects on disease progression (Phase 3, NCT04315948) (31) • Early treatment with RDV resulted in 87% lower risk of hospitalization or death (Phase 3, NCT04501952) (32) • Early treatment with RDV significantly reduced the rate of hospitalization (33)
Molnupiravir (MOV)	Viral RdRp	**FDA EUA (December 2021)**: Patients with mild-to-moderate COVID-19 at high risk for progression to severe COVID-19 (age: ≥18 years) **EMA**: Under evaluation	• MOV is well tolerated and has good dose-proportional pharmacokinetics among healthy individuals (Phase 1, NCT04392219) (53) • MOV accelerated viral RNA clearance (Phase 2, NCT04405570) (54) • MOV is effective in disrupting COVID-19 progression when given early into disease course (Phase 3, MOVe-OUT, NCT04575597) (55)
Nirmatrelvir + ritonavir	3CL-pro	**FDA EUA (December 2021)**: Patients with mild-to-moderate COVID-19 at high risk for progression to severe COVID-19 (age: ≥18 years) **EMA conditional approval (January 2022)**: Adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19	• Treatment with nirmatrelvir plus ritonavir reduced the risk of progression to severe COVID-19 by 89% against placebo (Phase 2-3, EPIC-HR trial, NCT04960202) (68) • Treatment with nirmatrelvir reduced the risk of long COVID, post-acute hospitalization, and post-acute death regardless of vaccination status and history of prior infection of the participants (70) • SARS-CoV-2 clearance was observed in 92.5% of participants in the nirmatrelvir group (Phase 3, NCT05341609) (71)
Sofosbuvir (SOF)	Viral RdRp	**No FDA/EMA approval**	• SOF/DCV did not cause significant symptom alleviation. SOF/DCV significantly reduced the number of patients with fatigue and dyspnea after 30 days (IRCT20200403046926N1) (86) • SOF/DCV provided no significant protective effect (COVER trial) (88) • SOF/VEL treatment resulted in SARS-CoV-2 clearance in 50% and 80% of cases within 7 and 14 days, respectively (84) • SOF/VEL treatment in patients with moderate to severe COVID-19 resulted in no improvement in clinical status nor mortality rates (85)
Camostat mesylate/ Nafamostat mesylate	TMPRSS2	**No FDA/EMA approval**	• Camostat mesylate treatment significantly lowered hospital mortality rate and need for invasive mechanical ventilation (92) • Treatment with camostat mesylate did not significantly improve clinical outcomes (Phase 2) (93) • Time to clinical improvement of patients treated with camostat mesylate was not significantly different compared to placebo (Phase 2) (89) • Treatment with nafamostat mesylate was poorly tolerated and had additional adverse effects compared to SOC (Phase 1b/2a, NCT04473053) (97) • Nafamostat treatment in hospitalized patients with moderate to severe COVID-19 did not result in significant difference in time to clinical improvement compared to SOC (NCT04623021) (98)

Several *in vitro* studies have shown the effectivity of RDV against SARS-CoV-2 (22-24). In a non-human primate model, early treatment with RDV produced no evidence of SARS-CoV-2-related respiratory disease (25). Similarly, prophylactic RDV treatment inhibited MERS-CoV replication in respiratory tissues of rhesus macaques (26).

To evaluate the clinical efficacy and safety of RDV, the Adaptive Covid-19 Treatment Trial (ACTT1, NCT04280705), a phase 3, double-blind, randomized, placebo-controlled study, randomly assigned 1,062 adult COVID-19 patients to receive either intravenously administered RDV (n=541) or placebo (n=521) (27). This study reported that patients who received RDV had a shorter time of recovery compared to those who received placebo (median, 10 vs. 15 days). By day 15, the Kaplan–Meier estimates of mortality with RDV is

lower than with placebo (6.7% vs. 11.9%). Patients who received RDV treatment were also more likely to have clinical improvement compared to those who received placebo within the same timeframe. Overall, the results imply that treatment with RDV prevented the development of a more severe disease, reduced disease burden, and decreased the need for health care resources (i.e., ventilator) among adults who were hospitalized with COVID-19.

Gilead Sciences, the makers of RDV, also initiated two clinical trials to determine the efficacy of RDV treatment in patients with moderate and severe COVID-19. NCT04292899, a phase 3, randomized, open label clinical trial compared 5- and 10-day courses of intravenous RDV to severe COVID-19 patients (28). Based on the results, there was no significant difference in efficacy between a 5- and a 10-day course of RDV. Besides, the trial was not placebo-controlled, hence the effectivity of RDV itself was not assessed. Similarly, in a phase 3, randomized, open label study (NCT04292730), patients with moderate COVID-19 were subjected to 5 or 10 days of RDV treatment or standard of care (SOC) (29). No statistically significant difference in clinical status between the 10-day RDV treatment and SOC was observed. On the other hand, patients in the 5-day treatment group had significantly higher odds of having better clinical distribution 11 days after treatment initiation. The open-label study design of both trials may be unsuitable for examining the efficacy and safety of RDV as such study designs can be prone to biases, particularly in decisions involving patient care and data reporting (30).

The WHO Solidarity trials (NCT04315948; phase 3, randomized, open label) evaluated the clinical efficacy and safety of various repurposed antiviral drugs including RDV. Based on the results, RDV treatment produced no significant impact on COVID-19 patients who were already receiving ventilation, and had minimal effects on disease progression of other hospitalized patients (31).

A phase 3, randomized, double-blind, placebo-controlled clinical trial (NCT04501952) recruited non-hospitalized COVID-19 patients with symptom onset within the past week and at least one risk factor for disease progression (32). Patients were randomly assigned to receive either intravenous RDV (n=279) or placebo (n=283). The primary efficacy endpoint of the study was hospitalization due to COVID-19 or death by day 28. A 3-day course of RDV exhibited a good safety profile. Interestingly, the study revealed that early treatment with RDV yielded an 87% lower risk of hospitalization or death among non-hospitalized patients compared to placebo.

RDV also showed efficacy against certain sublineages of the Omicron variant. In a prospective observational study, the impact of RDV to the rate of hospitalization was assessed among outpatient solid organ transplant recipients (SOTr) (33). The study was conducted in April to May 2022 during the Omicron BA.2 wave in Ontario, Canada. Of the 192 SOTr participants, 86 (44.8%) received RDV within 7 days of symptom onset. The results showed that early treatment with RDV significantly reduced the rate of hospitalization. Also, no patient who received RDV required intensive care unit (ICU) admission or passed away. In another study, Takashita et al. (34) tested the efficacy of RDV and other antiviral agents against Omicron BA.2.12.1, BA.4, and BA.5 subvariants. The *in vitro* evaluation of the authors revealed that the BA.2.12.1, BA.4, and BA.5 sublineages are susceptible to RDV treatment (34). Similarly, Imai et al. (35) showed that RDV is efficacious against a more recent rapidly spreading Omicron subvariants, BQ.1.1 and XBB.

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RDV treatment shows a lot of promise for preventing the progression of COVID-19 when used early despite having mixed clinical trial results. Currently, it is the only antiviral with full approval for treatment against COVID-19 from both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (36,37). However, it is not without its own caveats. For one, a full course of RDV is difficult to administer, making prescription of RDV impractical to some since other more promising and more accessible treatments are available (38).

More studies are still needed to further verify the efficacy and safety of RDV. Several trials involving RDV are yet to be completed (NCT04321616, NCT04314817, and NCT04315948).

Molnupiravir

Molnupiravir (EIDD-2801, MK-4482, and MOV [Lagrevio™]; Merck, Rahway, NJ, USA) is an orally bioavailable prodrug of the ribonucleoside analogue β-D-N4-hydroxycytidine (NHC) (39). Upon distribution to cells, NHC is phosphorylated to its active compound NHC 5'-triphosphate (NHC-TP) which acts as a competitive substrate for the RdRp (40). The antiviral effect of MOV is based on the incorporation of NHC-TP by RdRp into the nascent viral RNA chain, resulting in the accumulation of errors in the viral genome and the inhibition of viral replication (41,42).

Before the COVID-19 pandemic, MOV was initially recommended as a clinical candidate for treating seasonal influenza virus infection (43). Pre-clinical studies also highlighted its antiviral activity against a broad-spectrum of RNA viruses, including flaviviruses (e.g., hepatitis C virus [HCV] and bovine viral diarrhea virus); alphaviruses (e.g., chikungunya virus and Venezuelan equine encephalitis virus); filoviruses (e.g., Ebola virus and Marburg virus); and coronaviruses (e.g., SARS-CoV and MERS-CoV) (44-49). In a cell-based assay, Zhao et al. (50) revealed the inhibitory effects of MOV on the SARS-CoV-2 RdRp with a half-maximal effective concentration of 0.22 μM. In animal models, MOV significantly reduced the SARS-CoV-2 load in the upper respiratory tract of ferrets, while treatment in Syrian hamsters reduced viral RNA copy numbers and infectious virus titers in the lungs (51,52).

Presently, results for three completed clinical trials for MOV have been posted (**Table 1**). One of these studies, a phase 1 double-blind, placebo-controlled, first-in-human, randomized trial (NCT04392219) evaluated the safety, tolerability, and pharmacokinetics of MOV after oral administration to healthy volunteers (53). The results suggest that MOV is well tolerated and has a good dose-proportional pharmacokinetics among healthy individuals. Following this study, a phase 2a double-blind, placebo-controlled, randomized trial (NCT04405570) measured the time of SARS-CoV-2 viral RNA clearance to evaluate the antiviral efficacy of MOV in unvaccinated participants with symptomatic COVID-19 infection (54). In this trial, participants administered with 800 mg of MOV exhibited accelerated viral RNA clearance (median, 14 days) compared to those administered placebo (median, 27 days). Recently, the MOVe-OUT trial, a phase 3 double-blind, placebo-controlled, randomized study (NCT04575597), was designed to evaluate the efficacy and safety of MOV in non-hospitalized, unvaccinated adults against placebo (55). The MOVe-OUT trial results revealed that when administered within 5 days of symptom onset, 800 mg of MOV is safe and efficacious in reducing the risk of hospitalization or death among non-hospitalized, unvaccinated adults. The results of these trials strongly suggest that MOV is effective in disrupting COVID-19 progression when given early into the disease course.

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Since November 2021, the EMA has advised against the use of MOV during pregnancy or breastfeeding. Although no studies have evaluated its safety and efficacy in pregnant women, the EMA cited the reproductive toxicity of MOV in pregnant rats, which is characterized by embryo-fetal lethality, teratogenicity, and reduced fetal growth following oral administration of MOV (56). Currently, MOV is still under evaluation by the EMA (56). Additionally, WHO only recommends the drug to non-severe COVID-19 patients with the highest risk of hospitalization. WHO further advises against the use of MOV for children and adolescents less than 18 years of age due to the risk of bone and cartilage toxicity (57). The FDA, however, issued an emergency use authorization (EUA) for MOV for the treatment of mild-to-moderate COVID-19 in adult patients at high risk for progression to severe COVID-19 (58). More research should be done to establish a more comprehensive safety profile for MOV. Most recently, an open label randomized multicenter comparative phase 3 study (NCT05595824) was completed. The trial evaluated the efficacy and safety of MOV treatment in adult patients with COVID-19 as compared to SOC. As of the time of writing, the results of the trial are yet to be posted.

In an observational study in Hong Kong, the effectiveness of MOV was evaluated in non-hospitalized COVID-19 patients during the period when Omicron BA.2.2 subvariant was dominant (59). MOV treatment was associated with lower risk of mortality and lower risk of in-hospital disease progression as compared to non-treatment. MOV also exhibited activity against Omicron sublineages BA.2.12.1, BA.4, BA.5, BQ.1.1, and XBB *in vitro* (34,35). More clinical trials should be done to assess the efficacy of MOV against the currently circulating Omicron subvariants. Several clinical trials involving MOV have been registered (e.g., NCT05459532, NCT05412173, NCT04746183, NCT05195060, NCT04381936, NCT05013632, NCT05596045, NCT05041907, and NCT05271929).

Nirmatrelvir + ritonavir

During the 2002–2003 SARS-CoV outbreak, Pfizer (New York, NY, USA) developed PF-00835231 to inhibit the SARS-CoV 3CL-pro, a virally encoded protease critical for transcription and viral replication (60,61). The 3CL-pro active site is highly conserved among coronaviruses, making it a promising target for antivirals (62). PF-00835231 has also been reported to be effective against SARS-CoV-2 *in vitro* (63). However, due to its poor oral absorption, a more orally bioavailable nirmatrelvir (PF-07321332) was developed (64). Nirmatrelvir is co-administered with ritonavir (Paxlovid™; Pfizer) for treatment and post-exposure prophylaxis of COVID-19 (65). Similar to PF-00835231, nirmatrelvir blocks the activity of 3CL-pro and consequently inhibits viral replication (64). It is metabolized by the P450 cytochrome enzyme CYP3A4 in humans (66). Ritonavir then inactivates CYP3A4 and slows the metabolism of nirmatrelvir, allowing nirmatrelvir to remain in the body for a longer period of time (67).

In an *in vitro* study, nirmatrelvir inhibited SARS-CoV-2 replication in differentiated normal human bronchial epithelial cells treated with varying doses of nirmatrelvir for 3 days (64). In a phase 2–3 double-blind, randomized, controlled trial (EPIC-HR trial, NCT04960202), treatment with nirmatrelvir plus ritonavir reduced the risk of progression to severe COVID-19 by 89% compared to placebo (**Table 1**). The trial enrolled a total of 2,246 non-hospitalized, unvaccinated, symptomatic adults with symptom onset of no more than 5 days and randomly assigned them to receive either 300 mg of nirmatrelvir + 100 mg of ritonavir (n=1,120) or placebo (n=1,126) (68). Details about the SARS-CoV-2 variants involved in the trial were not reported. However, the incidence of Omicron among the trial subjects is expected to

be minimal as the first Omicron cases were diagnosed just a few days after the end of trial enrollment (69).

In a preprint, Xie et al. (70) revealed that treatment with nirmatrelvir during the acute phase of COVID-19 reduces the risk developing long COVID or post-acute sequelae of SARS-CoV-2 infection. The study involved participants who tested positive from SARS-CoV-2 between 2022 March 01 and 2022 June 30. Participants who received nirmatrelvir within 5 days of diagnosis were listed into the nirmatrelvir group (n=9,217), while those who did not receive any antiviral or antibody treatment within 30 days after diagnosis were enrolled into the control group (n=47,123). Aside from reducing the risk of long COVID, treatment with nirmatrelvir also reduced post-acute hospitalization and post-acute death regardless of vaccination status and history of prior infection of the participants (70).

During the outbreak off the Omicron variant of SARS-CoV-2 in Shanghai, China, a phase 3, observer-blinded, randomized trial (NCT05341609) was conducted to compare the safety and efficacy of nirmatrelvir and VV116, an oral antiviral agent (71). The trial enrolled a total of 822 symptomatic adults with mild-to-moderate COVID-19 and high risk of disease progression. By day 14, SARS-CoV-2 clearance was observed in 92.5% of participants in nirmatrelvir group and 94.8% of participants in the VV116 group. SARS-CoV-2 genomic analysis also showed that the BA.2.2 sublineage was present in all 129 patient samples tested, indicating that the major variant involved during the trial was Omicron. Along with RDV and MOV, nirmatrelvir may have therapeutic effects against the BA.2.12.1, BA.4, BA.5, BQ.1.1, and XBB sublineages of SARS-CoV-2 (34,35). Nirmatrelvir is also associated with lower risk of death, hospitalization, and in-hospital disease progression compared to non-use in patients infected with Omicron BA.2.2 variant (59). Nirmatrelvir plus ritonavir already received an EUA in the USA, UK, Australia, EU, and Canada (72-76). The clinical trials aiming to assess the efficacy of nirmatrelvir plus ritonavir in patients under 18 years of age (NCT05261139), immunocompromised patients >12 years of age (NCT05438602), pregnant patients (NCT05386472), and for treatment of long COVID (NCT05576662) are still recruiting.

Sofosbuvir (SOF)

SOF (Sovaldi®; Gilead Sciences) is a nucleotide analogue RdRp inhibitor primarily used in combination with other drugs for the treatment of HCV infection (77). SOF also exhibits antiviral activity against other positive-sense single-stranded RNA viruses including flaviviruses, such as dengue virus and Zika virus, and an alphavirus, namely chikungunya virus (78-80). Due to the similarities in replication mechanisms between HCV and coronaviruses, SOF is being considered a prospective antiviral candidate against SARS-CoV-2 (81). Results of an *in silico* study suggested that SOF tightly binds the active site of the SARS-CoV-2 RdRp (82). This binding consequently terminates further RNA chain extension and replication of SARS-CoV-2 (81). Jockusch et al. (83) also found that SARS-CoV-2 RNA terminated by SOF is more resistant to proofreading than the strand terminated by RDV.

The safety and efficacy of SOF treatment in combination with velpatasvir (VEL) was evaluated in patients with mild or moderate COVID-19 in a multicenter case control study (**Table 1**) (84). Enrolled patients were assigned to receive either SOF/VEL treatment (n=30) within 6 days after infection or SOC (n=90). Treatment with SOF/VEL exhibited SARS-CoV-2 clearance in 50% and 80% of cases within 7 and 14 days, respectively. This is in contrast with the SOC group where only 1.1% and 13% of cases showed viral clearance within 7 and 14

days, respectively. Additionally, no patients treated with SOF/VEL had disease progression (requirement of high-flow oxygen and ventilation), while 24% of patients receiving SOC progressed to conditions that required more intensive treatment. In contrast, Sayad et al. (85) found that treatment of SOF/VEL in patients with moderate to severe COVID-19 showed no improvement in clinical status nor mortality rates in a randomized, open-labelled, prospective clinical trial. Although both studies suggest that early treatment with SOF/VEL is safe, a larger randomized trial is needed to further verify its efficacy.

In a double-blind, randomized controlled clinical trial in outpatients with mild COVID-19 (IRCT20200403046926N1), SOF in combination with daclatasvir (DCV) plus hydroxychloroquine (HCQ, n=27) was evaluated vs HCQ alone (n=28) (86). The primary and secondary endpoints of the trial were symptom alleviation after 7 days and hospital admission, respectively. No significant difference in symptom alleviation was observed at day 7 between the SOF/DCV and HCQ groups. Although not statistically significant, treatment with SOF/DCV had fewer incidence of hospitalization. Meanwhile, a month after enrollment, SOF/DCV significantly reduced the number of patients with fatigue and dyspnea. As both symptoms are indications of long COVID, these results suggest that treatment with SOF/DCV may help reduce the risk of developing long COVID (87). Further randomized controlled trial (RCT) studies with larger sample sizes must be conducted to draw firm conclusions about the effectiveness of SOF/DCV in treating COVID-19.

In the recent COVER trial, the ability SOF/DCV to lower the risk of SARS-CoV-2 infection was evaluated during the Omicron wave in Johannesburg, South Africa (88). It was found that SOF/DCV provided no significant protective effect in healthcare workers at high risk of SARS-CoV-2 infection. Several trials involving SOF in COVID-19 are still ongoing.

Camostat mesylate and nafamostat mesylate

Camostat mesylate (Foipan®; Ono Pharmaceutical, Osaka, Japan) is a serine protease inhibitor approved in Japan for treatment of chronic pancreatitis and postoperative reflux esophagitis (89). It inhibits the activity of TMPRSS2 and, in turn, restricts entry of SARS-CoV-2 into the host cell as demonstrated by Hoffman et al. (90) using Calu-3 cells derived from human lung epithelial cells. In a mouse model, camostat mesylate prevented SARS-CoV spread and pathogenesis (91). Treatment with camostat mesylate was assessed by Sakr et al. (92) in a retrospective analysis of 371 adult patients with COVID-19 pneumonia admitted to ICU. Patients (n=141, 38%) were given 200 mg camostat mesylate three times daily for 7 days upon admission to ICU (**Table 1**). Both the ICU/hospital mortality rate and need for invasive mechanical ventilation were significantly lower in patients treated with camostat mesylate. Gunst et al. (93) evaluated the efficacy and safety of camostat mesylate in a phase 2 double-blind, randomized, placebo-controlled, multicenter trial. Participants were randomly assigned to receive either 200 mg camostat mesylate three times daily for 5 days (n=137) or placebo (n=68). Results revealed that treatment with camostat mesylate did not significantly improve clinical outcomes (time to clinical improvement, risk of intubation or death, time to discontinuation of supplemental oxygen). Tobback et al. (89) also conducted a phase 2 randomized, controlled trial in COVID-19 patients. The findings revealed that 300 mg of camostat mesylate three times daily for 5 or 10 consecutive days is not effective against SARS-CoV-2. However, a phase 2, double-blind, randomized, placebo-controlled trial revealed that early treatment with camostat mesylate prevented the loss of smell/taste and reduced the duration of illness in COVID-19 adult outpatients (94).

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Nafamostat mesylate (Futhan®; Torii Pharmaceutical, Tokyo, Japan), a similar serine protease inhibitor, was also reported to block SARS-CoV-2 entry by targeting TMPRSS2 (95,96). A phase 1b/2a randomized controlled trial tested the safety of intravenous nafamostat mesylate administration vs SOC in hospitalized patients with COVID-19 pneumonitis (NCT04473053) (97). In the trial, treatment with nafamostat mesylate was poorly tolerated and had additional adverse effects compared to SOC. Moreover, a randomized phase 2 clinical trial found that nafamostat treatment in hospitalized patients with moderate to severe COVID-19 did not produce any significant difference in time to clinical improvement compared to SOC (NCT04623021) (98).

Further clinical trials are needed to confirm the efficacy of camostat mesylate treatment against COVID-19. Moreover, although camostat mesylate may effectively block TMPRSS2 activity, it should be noted that SARS-CoV-2 can still utilize the clathrin-mediated pathway to infect host cells in the absence of TMPRSS2. Thus, combined treatment that blocks both SARS-CoV-2 entry pathways should be considered. However, a clinical trial looking to evaluate the efficacy of camostat mesylate + HCQ was withdrawn due to lack of public funding and unsatisfactory results of HCQ treatment in other studies (NCT04338906).

IMMUNE-BASED THERAPIES

SARS-CoV-2-neutralizing antibody products

Bebtelovimab

Bebtelovimab (LY-CoV1404; AbCellera [Vancouver, Canada] and Eli Lilly [Indianapolis, IN, USA]) is a SARS-CoV-2-neutralizing human IgG1 monoclonal Ab (mAb) isolated from a donor who recently recovered from COVID-19 (up to 60 days after symptom onset) (99). It binds to the RBD of the SARS-CoV-2 S protein, overlapping the ACE2-binding domain, preventing the virus from binding to its receptor and thereby inhibiting virus entry into the target cell (**Table 2**) (99). Pseudovirus neutralization studies by Westendorf et al. (99) revealed that bebtelovimab potently neutralizes a broad spectrum of SARS-CoV-2 variants, including Omicron and its sublineages. Moreover, a phase 2, randomized, double-blinded, placebo-controlled clinical trial (BLAZE-4 trial, NCT04634409) revealed that treatment with bebtelovimab (as monotherapy or in combination with bamlanivimab and etesevimab) is associated with increased viral clearance and faster symptom resolution (100). This study, however, was conducted before the emergence of the Omicron variant (B.1.1.529). In February 2022, based on these evidences, FDA issued an EUA for bebtelovimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients (>12 years of age) who are at high risk for progression to severe COVID-19 (101). In a recent study, the safety and efficacy of bebtelovimab were tested in outpatients with COVID-19 who were unable to receive the oral antiviral treatment, nirmatrelvir plus ritonavir. Results showed that bebtelovimab treatment decreased the risk of hospitalization or death, making it a good substitute for nirmatrelvir (102). However, on November 2022, FDA reported that bebtelovimab had reduced activity against emerging Omicron subvariants BQ.1 and BQ.1.1 (103). Imai et al. (35) also found that bebtelovimab had no efficacy against BQ.1.1 and XBB subvariants in an *in vitro* study. Given the lack of neutralizing activity against different Omicron subvariants, FDA announced that bebtelovimab is no longer authorized for emergency use in the US (104).

Tixagevimab/Cilgavimab

Tixagevimab/cilgavimab (AZD7442, Evusheld™, AstraZeneca, Cambridge, UK) is a

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Table 2. Summary of clinical studies and approvals for immune-based COVID-19 treatments

Immune-based treatment	Target	FDA/EMA approval	Findings
Bebtelovimab	S-protein	**FDA EUA (February 2022)**: Patients with mild-to-moderate COVID-19 at high risk for progression to severe COVID-19 (age: ≥18 years) **FDA (November 2022)**: Expected reduced activity against certain Omicron subvariants	• Bebtelovimab potently neutralizes a broad spectrum of SARS-CoV-2 variants, including Omicron and its sublineages (99) • BLAZE-4 trial - Bebtelovimab is associated with increased viral clearance and faster symptom resolution (Phase 2, BLAZE-4 trial, NCT04634409) (100) • Bebtelovimab decreased the risk of hospitalization or death (102)
Tixagevimab/ cilgavimab (AZD7442)	S-protein	**No longer authorized by the FDA (January 2023)** **EMA marketing authorization (December 2021)**: Prevention of COVID-19 (age: ≥12 years; weight: ≥40 kg)	• AZD7442 demonstrated efficacy in preventing COVID-19 infection in adult participants (Phase 3, PROVENT trial, NCT04625725) (105) • Reduced efficacy against the Omicron variant (B.1.1.529) (109,110)
Bamlanivimab/ etesevimab	S-protein	**FDA EUA (January 2022)**: Patient likely to have been infected with or exposed to a susceptible variant	• Bamlanivimab/etesevimab treatment associated with 70% reduction in COVID-19-related hospitalization or death against placebo (Phase 3) (114) • Highly unlikely to be active against the Omicron variant (113)
Casirivimab/ Imdevimab (REGEN-COV)	S-protein	**FDA EUA (January 2022)**: Patient likely to have been infected with or exposed to a susceptible variant	• Significant reduction in viral load among patients treated with REGEN-COV (116) • Reduced 28-day mortality in seronegative patients (118) • Highly unlikely to be active against the Omicron variant (119)
Regdanvimab (CT-P59)	S-protein	**EMA marketing authorization (November 2021)**: Patients who do not require supplemental oxygen and who are at high-risk of progressing to severe COVID-19	• Treatment with CT-P59 shortened time to recovery, hastened viral load reduction, and lowered the portion of COVID-19 patients with disease progression (Phase 3, NCT04602000) (121)
Sotrovimab	S-protein	**No longer authorized by the FDA (April 2022)**	• Sotrovimab reduced the risk of disease progression among patients with mild-to-moderate COVID-19 (Phase 3, COMET-ICE trial, NCT04545060) (125) • Unlikely to be effective against the BA.2 subvariant (126)
Tocilizumab	IL-6	**FDA EUA (June 2021)**: Hospitalized pediatric patients (2-17 years) who are receiving systemic corticosteroids and require supplemental oxygen, mechanical ventilation, or ECMO **FDA approval (December 2022)**: Hospitalized adult patients (≥18 years) who are receiving systemic corticosteroids and require supplemental oxygen, mechanical ventilation, or ECMO **EMA conditional approval (January 2022)**: Patients receiving treatment with corticosteroid medicines by mouth or injection and require extra oxygen or mechanical ventilation	• Treatment with tocilizumab in critically ill COVID-19 patients improved clinical outcomes including survival (REMAP-CAP trial, NCT02735707) (133) • Tocilizumab improved survival and other clinical outcomes (RECOVERY trial, NCT04381936) (134) • Tocilizumab treatment of patients with severe COVID-19 pneumonia did not significantly improve clinical status or survival of patients vs. placebo (135)
Anakinra	IL-1	**FDA EUA (November 2022)**: Hospitalized adults (≥18 years) requiring supplemental oxygen and are at risk of severe respiratory failure	• suPAR-guided treatment with anakinra significantly reduced the risk of worse clinical outcomes in patients with moderate and severe COVID-19 (141).
Baricitinib	JAK1/2	**FDA approved for treatment (May 2022)**: Hospitalized adults requiring supplemental oxygen, mechanical ventilation, or ECMO **EMA conditional approval (January 2022)**: Adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID 19	• Patients who received baricitinib plus RDV had reduced recovery time and accelerated improvement in clinical status compared to those who received RDV alone (NCT04401579) (148)
Dexamethasone (Corticosteroid)	Anti-inflammatory	**EMA conditional approval (September 2020)**: Adults and adolescent patients (age: ≥12 years; weight: ≥40 kg) requiring supplemental oxygen therapy	• Dexamethasone treatment resulted in lower 28-day mortality among hospitalized COVID-19 patients receiving ventilation (RECOVERY trial, NCT04381936) (153)

combination of 2 SARS-CoV-2–neutralizing monoclonal antibodies derived from B cells of persons previously infected with COVID-19. AZD7442 neutralizes SARS-CoV-2 by binding to distinct nonoverlapping epitopes of S protein RBD, which blocks RBD binding with ACE2 and essentially prohibiting SARS-CoV-2 entry into host cells (105). This two-antibody cocktail showed efficacy in preventing and treating SARS-CoV-2 infections *in vivo* (106,107). In a phase 3, multicenter, double-blind, parallel-group, randomized, placebo-controlled

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PROVENT clinical trial (NCT04625725), AZD7442 demonstrated efficacy in preventing COVID-19 infection in adult participants (**Table 2**). In this trial, a total of 5,197 participants were randomized to receive either one dose of AZD7442 (n=3,460) or placebo (n=1,737) (105). Results revealed that a single dose of AZD7442 reduced the risk of developing symptomatic SARS-CoV-2 infection by 77%. In addition, no cases of severe COVID-19 or death were reported among participants treated with AZD7442 (108).

Previously, AZD7442 was the only therapeutic with EUA for pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (>12 years of age) (109). However, an *in vitro* study showed that tixagevimab/cilgavimab had reduced efficacy against the B.1.1.529 Omicron variant (110). FDA also revealed that tixagevimab/cilgavimab have reduced neutralizing activity against several Omicron sublineages (109). In January 2023, FDA revised the EUA for AZD7442 and limited its use to only when the combined frequency of non-susceptible SARS-CoV-2 variants in the US is less than or equal to 90% (111).

Bamlanivimab (BAM)/etesevimab (ETE)

BAM (LY-CoV555; Eli Lilly) and ETE (LY-CoV016; Eli Lilly) are SARS-CoV-2-neutralizing mAbs that bind overlapping epitopes of the SARS-CoV-2 S protein RBD to prevent viral attachment (112). BAM was the first authorized therapeutic neutralizing mAb against COVID-19 (113). In the BLAZE-1 phase 3 trial, treatment with BAM/ETE exhibited a 70% reduction in COVID-19-related hospitalization or death against placebo (**Table 2**) (114). However, in April 2021, the EUA for BAM was revoked following the decreased binding of BAM/ETE to the Beta and Gamma variants (113).

Casirivimab/imdevimab

Casirivimab/imdevimab (REGEN-COV™; Regeneron, Tarrytown, NY, USA) is a combination of two neutralizing IgG1 mAbs that non-competitively bind to non-overlapping epitopes of the RBD (6XDG), thereby blocking viral attachment and entry to host cell (112,115). In November 2020, it received its first EUA from FDA for the treatment of COVID-19 based on a randomized, placebo-controlled trial that demonstrated significant reduction in viral load among patients treated with REGEN-COV (**Table 2**) (116,117). The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial also showed that REGEN-COV reduced the 28-day mortality of seronegative patients (118). The EUA was eventually limited by FDA in January 2022 following studies showing that REGEN-COV is not active against the Omicron variant (119).

Regdanvimab

Regdanvimab (CT-P59; Celltrion, Incheon, Korea) is a neutralizing mAb against SARS-CoV-2 identified through screening of an antibody library made from peripheral blood mononuclear cells of a recovering SARS-CoV-2 patient (120). CT-P59 interferes with ACE2 receptor by blocking areas of the ACE2-interacting regions of SARS-CoV-2 RBD (120). In an *in vivo* study, CT-P59 reduced viral titers and alleviated clinical signs in golden Syrian hamster, ferret, and rhesus monkey animal models (120). A phase 3 double-blind, randomized clinical trial (NCT04602000) evaluated the clinical effectiveness of CT-P59 in mild-to-moderate COVID-19 outpatients (**Table 2**) (121). Results showed that treatment with CT-P59 shortened time to recovery, hastened viral clearance, and reduced the likelihood of disease progression (121). In November 2021, EMA authorized CT-P59 for the treatment of adult COVID-19 patients who do not require supplemental oxygen and who are at high-risk of progressing to severe COVID-19 (122). However, studies revealed that CT-P59 produced no neutralizing activity against the Omicron variant (110,123).

Sotrovimab

Sotrovimab (VIR-7831, Xevudy; GlaxoSmithKline [Brentford, UK] and Vir Biotechnology, Inc. [San Francisco, CA, USA]) is a SARS-CoV-2-neutralizing mAb that received its FDA EUA for the treatment of COVID-19 in May 2021 (124). Sotrovimab blocks viral entry by binding to the RBD of SARS-CoV-2 S protein. However, sotrovimab does not directly compete with ACE2 receptor as the antibody binds outside the binding motif of RBD (124). In the phase 3 COMET-ICE trial (NCT04545060), sotrovimab reduced the risk of disease progression among patients with mild-to-moderate COVID-19 (**Table 2**) (125). In March 2022, FDA limited the authorization for sotrovimab due to ineffectivity against the Omicron BA.2 variant (126).

Cytokine inhibitors

Tocilizumab

Tocilizumab (Actemra®; Genentech, South San Francisco, CA, USA) is a recombinant humanized monoclonal antibody indicated primarily for rheumatoid arthritis (127). It targets IL-6, a proinflammatory cytokine that can cause cytokine storm or cytokine release syndrome (CRS) during infection (128,129). CRS is a major cause of morbidity in patients infected with MERS-CoV and SARS-CoV (130,131) and is also correlated with respiratory failure and acute respiratory distress syndrome (ARDS) in COVID-19 patients (132). IL-6 therefore is a promising therapeutic target against severe SARS-CoV-2 infection.

In the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP, NCT02735707), treatment with tocilizumab in critically ill COVID-19 patients improved clinical outcomes including survival (**Table 2**) (133). Tocilizumab treatment also improved survival and other clinical outcomes in the RECOVERY trial (NCT04381936) (134). However, a phase 3, randomized, placebo-controlled trial (NCT04320615) yielded different results, wherein tocilizumab treatment of patients with severe COVID-19 pneumonia did not significantly improve the clinical status or survival of patients when compared with placebo treatment (135). The difference in outcomes of these trials may be attributed to the different periods of time over which the trials were conducted and varying severity of inflammation between each patient (128). More research should be done to identify the best treatment strategy when using tocilizumab for COVID-19. In June 2021, FDA issued an EUA for tocilizumab for the treatment of COVID-19 in hospitalized pediatric and adult patients (>2 years old) receiving additional care (systemic corticosteroid, supplemental oxygen, or extracorporeal membrane oxygenation [ECMO]). More recently, in December 2022, FDA approved tocilizumab for the treatment of COVID-19 in adult patients (>18 years old) requiring additional care (136). Tocilizumab, however, remains authorized for emergency use in hospitalized pediatric COVID-19 patients (2–17 years old). With this, tocilizumab becomes the first FDA-approved monoclonal antibody treatment for COVID-19.

Anakinra

Anakinra (KINERET®; Swedish Orphan Biovitrum AB, Stockholm, Sweden) is a recombinant IL-1 receptor antagonist approved by FDA for the treatment of rheumatoid arthritis and other autoinflammatory disorders (137). The selective cytokine blockade by anakinra was hypothesized to be beneficial to patients with severe COVID-19 and cytokine storm presentation (138-140).

The soluble urokinase plasminogen activator receptor (suPAR)-guided Anakinra treatment for Validation of the risk and Early Management Of seveRE respiratory failure by COVID-19 (SAVE-MORE, NCT04680949) trial, a phase 3 double-blind, randomized, controlled trial,

evaluated the safety and efficacy of anakinra treatment in hospitalized patients with moderate to severe COVID-19 (**Table 2**) (141). The SAVE-MORE research group utilized suPAR serum levels as an early predictor of progression to severe respiratory failure in COVID-19 patients. All 594 patients in the analysis cohort had plasma suPAR ≥6 ng ml^{-1} and were randomized to receive either anakinra or placebo in addition to SOC. Results showed that suPAR-guided treatment with anakinra significantly reduced the risk of worse clinical outcomes in patients with moderate and severe COVID-19 (141). Considering the findings of the SAVE-MORE trial, in November 2022, the FDA issued an EUA for anakinra for the treatment of COVID-19 in hospitalized adults (≥18 years) requiring supplemental oxygen and are at risk of severe respiratory failure (142). The data collection date for primary outcome measures of the trial concluded before the first reported case of the Omicron variant. Thus, more trials are needed to evaluate the efficacy of anakinra in currently circulating Omicron sublineages.

Janus kinase (jak) inhibitor

Baricitinib

Baricitinib (Olumiant®; Eli Lilly) is an orally available JAK 1 and JAK 2-inhibitor used primarily for the treatment of rheumatoid arthritis (143). It was first identified as a potential therapeutic option for COVID-19 by artificial intelligence (AI) algorithms. The AI algorithm predicted candidate drugs that may inhibit both SARS-CoV-2 infectivity and SARS-CoV-2-induced inflammatory damage (144,145). As was predicted, baricitinib exhibited anti-cytokine and potential antiviral activities *in vitro* (145). Baricitinib inhibits the JAK-mediated release of pro-inflammatory cytokines, including IL-2, IL-6, IL-10, IFN-γ, and G-CSF, that are implicated in severe COVID-19 cases, which may explain its effects (146,147). Additionally, baricitinib had shown potent inhibition of Numb-associated kinases (NAK) that are essential to viral entry and propagation (145).

In a double-blind, randomized, placebo-controlled trial, the effects of baricitinib + RDV was evaluated in hospitalized adult COVID-19 patients (NCT04401579; **Table 2**) (148). Results revealed that COVID-19 patients who received baricitinib + RDV (n=515) had reduced recovery time and accelerated improvement in clinical status compared to those who received RDV alone (n=518). On May 2022, FDA authorized the emergency use of baricitinib to treat COVID-19 in hospitalized pediatric patients (2 to less than 18 years of age) requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO (149). More studies are still needed to evaluate its efficacy in currently circulating SARS-CoV-2 variants.

Anti-inflammatory agents

Corticosteroids

Early into the COVID-19 pandemic, corticosteroids were not recommended for use against COVID-19 based on the detrimental effects it may cause, as observed during the previous SARS-CoV and MERS-CoV outbreaks (150). Nonetheless, with more information on the pathophysiology of COVID-19, it was hypothesized that the anti-inflammatory properties of corticosteroids may suppress hyperinflammation and modulate the immune-mediated damages following SARS-CoV-2 infection (151). Dexamethasone (DEX), a glucocorticosteroid used primarily to treat inflammatory and autoimmune diseases, was found to dampen the inflammatory neutrophil response associated with severe COVID-19 *in vitro* (152). DEX was examined as treatment in a controlled, randomized, open-label RECOVERY trial (NCT04381936; **Table 2**) (153). The trial findings showed that treatment with dexamethasone resulted in a lower 28-day mortality among hospitalized COVID-19 patients receiving ventilation (n=2,104, 22.9%) as compared to patients with no respiratory support (n=4,321,

25.7%). Based on these results, in August 2020, EMA endorsed the use of dexamethasone only in adult and adolescent patients (≥12 years of age) who require supplemental oxygen therapy (154). Currently, no sufficient data is available to support or prohibit the use of systemic and inhaled corticosteroids in non-hospitalized COVID-19 patients. Even so, close monitoring of the patients under corticosteroid treatment is crucial due to the associated adverse effects such as hyperglycemia, secondary infections, and neuropsychiatric symptoms (155).

PERSPECTIVES AND CONCLUSIONS

The rapid spread of SARS-CoV-2 severely impacted global health and economy. As morbidity and mortality continued to rise especially among vulnerable populations, the development of preventive and therapeutic measures quickly became a priority. Global efforts in clinical research led to the identification of several therapeutic options. For antivirals, RDV remains the sole agent fully authorized for COVID-19 treatment. As is the case for direct-acting antivirals targeting acute viral diseases, the therapeutic value of RDV lies on its ability to inhibit viral replication and is generally most apparent when administered early into the COVID-19 disease course. The difficulty of RDV administration (intravenous), the lack of accessibility, and the requirement for early treatment continue to limit the use of RDV. On the other hand, preference for oral antivirals like nirmatrelvir + ritonavir is expected due to ease of administration. However, further studies on safety and efficacy are still needed before nirmatrelvir receives full approval as a SARS-CoV-2 antiviral.

Aside from antivirals, immunotherapies quickly gained a lot of attention as treatment against COVID-19. The ability of monoclonal antibodies to neutralize the virus has come in handy in inhibiting infection and progression to more severe disease. However, the emergence of new SARS-CoV-2 variants has rendered some potent treatments to lose effectivity. Consequently, clinical practices need to be constantly reviewed and shifted as new data from recently concluded studies and trials become available.

Although vaccination remains the most effective strategy in controlling SARS-CoV-2 infection, not all individuals are equally capable of producing adequate immune responses even after multiple vaccine doses. Some people also exhibit adverse reactions to vaccination. Antivirals and immune-based treatments not only provide alternative options to such individuals; continued improvements and discoveries in therapeutics also ensures that we are more equipped for future pandemics.

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REFERENCES

1. World Health Organization. WHO coronavirus (COVID-19) dashboard [Internet]. Available at https://covid19.who.int [accessed on 22 November 2022].
2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. Available at https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 [accessed on 22 November 2022].
3. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395:565-574.
PUBMED | CROSSREF
4. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, Yuen KY. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect* 2020;9:221-236.
PUBMED | CROSSREF
5. Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV--a target for vaccine and therapeutic development. *Nat Rev Microbiol* 2009;7:226-236.
PUBMED | CROSSREF
6. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631-637.
PUBMED | CROSSREF
7. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003;426:450-454.
PUBMED | CROSSREF
8. Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol* 2022;23:3-20.
PUBMED | CROSSREF
9. Abulsoud AI, El-Husseiny HM, El-Husseiny AA, El-Mahdy HA, Ismail A, Elkhawaga SY, Khidr EG, Fathi D, Mady EA, Najda A, et al. Mutations in SARS-CoV-2: insights on structure, variants, vaccines, and biomedical interventions. *Biomed Pharmacother* 2023;157:113977.
PUBMED | CROSSREF
10. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. *Nat Rev Microbiol* 2021;19:155-170.
PUBMED | CROSSREF
11. Snijder EJ, Decroly E, Ziebuhr J. The nonstructural proteins directing coronavirus RNA synthesis and processing. *Adv Virus Res* 2016;96:59-126.
PUBMED | CROSSREF
12. Anand K, Ziebuhr J, Wadhwani P, Mesters JR, Hilgenfeld R. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. *Science* 2003;300:1763-1767.
PUBMED | CROSSREF
13. Aftab SO, Ghouri MZ, Masood MU, Haider Z, Khan Z, Ahmad A, Munawar N. Analysis of SARS-CoV-2 RNA-dependent RNA polymerase as a potential therapeutic drug target using a computational approach. *J Transl Med* 2020;18:275.
PUBMED | CROSSREF
14. Chen J, Wang R, Wang M, Wei GW. Mutations strengthened SARS-CoV-2 infectivity. *J Mol Biol* 2020;432:5212-5226.
PUBMED | CROSSREF
15. Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, Ludden C, Reeve R, Rambaut A, et al.; COVID-19 Genomics UK (COG-UK) Consortium SARS-CoV-2 variants, spike mutations and immune escape. *Nat Rev Microbiol* 2021;19:409-424.
PUBMED | CROSSREF
16. Kim S, Nguyen TT, Taitt AS, Jhun H, Park HY, Kim SH, Kim YG, Song EY, Lee Y, Yum H, et al. SARS-CoV-2 Omicron mutation is faster than the chase: multiple mutations on spike/ACE2 interaction residues. *Immune Netw* 2021;21:e38.
PUBMED | CROSSREF
17. World Health Organization. Tracking SARS-CoV-2 variants [Internet]. Available at https://www.who.int/activities/tracking-SARS-CoV-2-variants [accessed on 23 November 2022].

18. Tegally H, Wilkinson E, Lessells RJ, Giandhari J, Pillay S, Msomi N, Mlisana K, Bhiman JN, von Gottberg A, Walaza S, et al. Sixteen novel lineages of SARS-CoV-2 in South Africa. *Nat Med* 2021;27:440-446.
PUBMED | CROSSREF

19. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, Hall MD. Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19. *ACS Cent Sci* 2020;6:672-683.
PUBMED | CROSSREF

20. Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, Götte M. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J Biol Chem* 2020;295:6785-6797.
PUBMED | CROSSREF

21. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, Leist SR, Pyrc K, Feng JY, Trantcheva I, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* 2017;9:eaal3653.
PUBMED | CROSSREF

22. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res* 2020;30:269-271.
PUBMED | CROSSREF

23. Pruijssers AJ, George AS, Schäfer A, Leist SR, Gralinksi LE, Dinnon KH 3rd, Yount BL, Agostini ML, Stevens LJ, Chappell JD, et al. Remdesivir inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice. *Cell Reports* 2020;32:107940.
PUBMED | CROSSREF

24. Choy KT, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KP, Chu DK, Chan MC, Cheung PP, Huang X, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res* 2020;178:104786.
PUBMED | CROSSREF

25. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J, van Doremalen N, Leighton I, Yinda CK, Pérez-Pérez L, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature* 2020;585:273-276.
PUBMED | CROSSREF

26. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, Scott D, Cihlar T, Feldmann H. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A* 2020;117:6771-6776.
PUBMED | CROSSREF

27. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, et al. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med* 2020;383:1813-1826.
PUBMED | CROSSREF

28. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med* 2020;383:1827-1837.
PUBMED | CROSSREF

29. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, Ogbuagu O, Malhotra P, Mullane KM, Castagna A, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA* 2020;324:1048-1057.
PUBMED | CROSSREF

30. Day RO, Williams KM. Open-label extension studies: do they provide meaningful information on the safety of new drugs? *Drug Saf* 2007;30:93-105.
PUBMED | CROSSREF

31. WHO Solidarity Trial Consortium. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet* 2022;399:1941-1953.
PUBMED | CROSSREF

32. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, Oguchi G, Ryan P, Nielsen BU, Brown M, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med* 2022;386:305-315.
PUBMED | CROSSREF

33. Solera JT, Árbol BG, Bahinskaya I, Marks N, Humar A, Kumar D. Short-course early outpatient remdesivir prevents severe disease due to COVID-19 in organ transplant recipients during the Omicron BA.2 wave. *Am J Transplant* 2023;23:78-83.
PUBMED | CROSSREF

34. Takashita E, Yamayoshi S, Simon V, van Bakel H, Sordillo EM, Pekosz A, Fukushi S, Suzuki T, Maeda K, Halfmann P, et al. Efficacy of antibodies and antiviral drugs against Omicron BA.2.12.1, BA.4, and BA.5 subvariants. *N Engl J Med* 2022;387:468-470.
PUBMED | CROSSREF

35. Imai M, Ito M, Kiso M, Yamayoshi S, Uraki R, Fukushi S, Watanabe S, Suzuki T, Maeda K, Sakai-Tagawa Y, et al. Efficacy of antiviral agents against omicron subvariants BQ.1.1 and XBB. *N Engl J Med* 2023;388:89-91.
PUBMED | CROSSREF

36. United States Food and Drug Administration. FDA's approval of Veklury (remdesivir) for the treatment of COVID-19—the science of safety and effectiveness [Internet]. Available at https://www.fda.gov/drugs/news-events-human-drugs/fdas-approval-veklury-remdesivir-treatment-covid-19-science-safety-and-effectiveness [accessed on 14 November 2022].

37. European Medicines Agency. Veklury [Internet]. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/veklury [accessed on 14 November 2022].

38. Huang P. Why remdesivir, a highly effective COVID treatment, is a last resort for providers. *NPR*. 7 February 2022; Sect. Shots - Health News.

39. Toots M, Plemper RK. Next-generation direct-acting influenza therapeutics. *Transl Res* 2020;220:33-42.
PUBMED | CROSSREF

40. Painter GR, Bowen RA, Bluemling GR, DeBergh J, Edpuganti V, Gruddanti PR, Guthrie DB, Hager M, Kuiper DL, Lockwood MA, et al. The prophylactic and therapeutic activity of a broadly active ribonucleoside analog in a murine model of intranasal venezuelan equine encephalitis virus infection. *Antiviral Res* 2019;171:104597.
PUBMED | CROSSREF

41. Yoon JJ, Toots M, Lee S, Lee ME, Ludeke B, Luczo JM, Ganti K, Cox RM, Sticher ZM, Edpuganti V, et al. Orally efficacious broad-spectrum ribonucleoside analog inhibitor of influenza and respiratory syncytial viruses. *Antimicrob Agents Chemother* 2018;62:e00766-18.
PUBMED | CROSSREF

42. Gordon CJ, Tchesnokov EP, Schinazi RF, Götte M. Molnupiravir promotes SARS-CoV-2 mutagenesis via the RNA template. *J Biol Chem* 2021;297:100770.
PUBMED | CROSSREF

43. Toots M, Yoon JJ, Cox RM, Hart M, Sticher ZM, Makhsous N, Plesker R, Barrena AH, Reddy PG, Mitchell DG, et al. Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia. *Sci Transl Med* 2019;11:eaax5866.
PUBMED | CROSSREF

44. Agostini ML, Pruijssers AJ, Chappell JD, Gribble J, Lu X, Andres EL, Bluemling GR, Lockwood MA, Sheahan TP, Sims AC, et al. Small-molecule antiviral β-d-*N*4-hydroxycytidine inhibits a proofreading-intact coronavirus with a high genetic barrier to resistance. *J Virol* 2019;93:e01348-19.
PUBMED | CROSSREF

45. Barnard DL, Hubbard VD, Burton J, Smee DF, Morrey JD, Otto MJ, Sidwell RW. Inhibition of severe acute respiratory syndrome-associated coronavirus (SARSCoV) by calpain inhibitors and β-D-N4-hydroxycytidine. *Antivir Chem Chemother* 2004;15:15-22.
PUBMED | CROSSREF

46. Ehteshami M, Tao S, Zandi K, Hsiao HM, Jiang Y, Hammond E, Amblard F, Russell OO, Merits A, Schinazi RF. Characterization of β-d-*N*4-hydroxycytidine as a novel inhibitor of chikungunya virus. *Antimicrob Agents Chemother* 2017;61:e02395-16.
PUBMED | CROSSREF

47. Reynard O, Nguyen XN, Alazard-Dany N, Barateau V, Cimarelli A, Volchkov VE. Identification of a new ribonucleoside inhibitor of Ebola virus replication. *Viruses* 2015;7:6233-6240.
PUBMED | CROSSREF

48. Stuyver LJ, Whitaker T, McBrayer TR, Hernandez-Santiago BI, Lostia S, Tharnish PM, Ramesh M, Chu CK, Jordan R, Shi J, et al. Ribonucleoside analogue that blocks replication of bovine viral diarrhea and hepatitis C viruses in culture. *Antimicrob Agents Chemother* 2003;47:244-254.
PUBMED | CROSSREF

49. Urakova N, Kuznetsova V, Crossman DK, Sokratian A, Guthrie DB, Kolykhalov AA, Lockwood MA, Natchus MG, Crowley MR, Painter GR, et al. β-d-*N*4-hydroxycytidine is a potent anti-alphavirus compound that induces a high level of mutations in the viral genome. *J Virol* 2018;92:e01965-17.
PUBMED | CROSSREF

50. Zhao J, Guo S, Yi D, Li Q, Ma L, Zhang Y, Wang J, Li X, Guo F, Lin R, et al. A cell-based assay to discover inhibitors of SARS-CoV-2 RNA dependent RNA polymerase. *Antiviral Res* 2021;190:105078.
PUBMED | CROSSREF

51. Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. *Nat Microbiol* 2021;6:11-18.
PUBMED | CROSSREF

52. Abdelnabi R, Foo CS, De Jonghe S, Maes P, Weynand B, Neyts J. Molnupiravir inhibits replication of the emerging SARS-CoV-2 variants of concern in a hamster infection model. *J Infect Dis* 2021;224:749-753.
PUBMED | CROSSREF

53. Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NC, Morin MJ, Szewczyk LJ, Painter GR. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. *Antimicrob Agents Chemother* 2021;65:e02428-20.
PUBMED | CROSSREF

54. Fischer WA 2nd, Eron JJ Jr, Holman W, Cohen MS, Fang L, Szewczyk LJ, Sheahan TP, Baric R, Mollan KR, Wolfe CR, et al. A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. *Sci Transl Med* 2022;14:eabl7430.
PUBMED | CROSSREF

55. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martín-Quirós A, Caraco Y, Williams-Diaz A, Brown ML, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med* 2022;386:509-520.
PUBMED | CROSSREF

56. European Medicines Agency. EMA issues advice on use of Lagevrio (molnupiravir) for the treatment COVID-19 [Internet]. Available at https://www.ema.europa.eu/en/news/ema-issues-advice-use-lagevrio-molnupiravir-treatment-covid-19 [accessed on 26 October 2022].

57. World Health Organization. WHO updates its treatment guidelines to include molnupiravir [Internet]. Available at https://www.who.int/news/item/03-03-2022-molnupiravir [accessed on 26 October 2022].

58. United States Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes additional oral antiviral for treatment of COVID-19 in certain adults [Internet]. Available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain [accessed on 29 November 2022].

59. Wong CK, Au IC, Lau KT, Lau EH, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. *Lancet* 2022;400:1213-1222.
PUBMED | CROSSREF

60. Hoffman RL, Kania RS, Brothers MA, Davies JF, Ferre RA, Gajiwala KS, He M, Hogan RJ, Kozminski K, Li LY, et al. Discovery of ketone-based covalent inhibitors of coronavirus 3CL proteases for the potential therapeutic treatment of COVID-19. *J Med Chem* 2020;63:12725-12747.
PUBMED | CROSSREF

61. Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, Zhang B, Li X, Zhang L, Peng C, et al. Structure of M^{pro} from SARS-CoV-2 and discovery of its inhibitors. *Nature* 2020;582:289-293.
PUBMED | CROSSREF

62. Ullrich S, Nitsche C. The SARS-CoV-2 main protease as drug target. *Bioorg Med Chem Lett* 2020;30:127377.
PUBMED | CROSSREF

63. Boras B, Jones RM, Anson BJ, Arenson D, Aschenbrenner L, Bakowski MA, Beutler N, Binder J, Chen E, Eng H, et al. Preclinical characterization of an intravenous coronavirus 3CL protease inhibitor for the potential treatment of COVID19. *Nat Commun* 2021;12:6055.
PUBMED | CROSSREF

64. Owen DR, Allerton CM, Anderson AS, Aschenbrenner L, Avery M, Berritt S, Boras B, Cardin RD, Carlo A, Coffman KJ, et al. An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19. *Science* 2021;374:1586-1593.
PUBMED | CROSSREF

65. Lamb YN. Nirmatrelvir plus ritonavir: first approval. *Drugs* 2022;82:585-591.
PUBMED | CROSSREF

66. Reis S, Metzendorf MI, Kuehn R, Popp M, Gagyor I, Kranke P, Meybohm P, Skoetz N, Weibel S. Nirmatrelvir combined with ritonavir for preventing and treating COVID-19. *Cochrane Database Syst Rev* 2022;9:CD015395.
PUBMED | CROSSREF

67. Pfizer. Pfizer's novel COVID-19 oral antiviral treatment candidate reduced risk of hospitalization or death by 89% in interim analysis of phase 2/3 EPIC-HR study [Internet]. Available at https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate [accessed on 19 November 2022].

68. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, Baniecki M, Hendrick VM, Damle B, Simón-Campos A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med* 2022;386:1397-1408.
PUBMED | CROSSREF

69. Gentile I, Scotto R, Schiano Moriello N, Pinchera B, Villari R, Trucillo E, Ametrano L, Fusco L, Castaldo G, Buonomo AR, et al. Nirmatrelvir/ritonavir and molnupiravir in the treatment of mild/moderate COVID-19: results of a real-life study. *Vaccines (Basel)* 2022;10:1731.
PUBMED | CROSSREF

70. Xie Y, Choi T, Al-Aly Z. Nirmatrelvir and the risk of post-acute sequelae of COVID-19. Preprint at https://www.medrxiv.org/content/10.1101/2022.11.03.22281783v1 (2022).
CROSSREF

71. Cao Z, Gao W, Bao H, Feng H, Mei S, Chen P, Gao Y, Cui Z, Zhang Q, Meng X, et al. VV116 versus nirmatrelvir-ritonavir for oral treatment of Covid-19. *N Engl J Med* 2023;388:406-417.
PUBMED | CROSSREF

72. European Medicines Agency. Paxlovid [Internet]. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid [accessed on 15 November 2022].

73. Medicines & Healthcare products Regulatory Agency. COVID-19 antiviral, Paxlovid, approved by UK regulator [Internet]. Available at https://www.gov.uk/government/news/oral-covid-19-antiviral-paxlovid-approved-by-uk-regulator [accessed on 19 November 2022].

74. Pfizer. Pfizer receives health canada authorization for COVID-19 oral treatment [Internet]. Available at https://www.pfizer.ca/Health_Canada_Approves_PAXLOVID [accessed on 19 November 2022].

75. Therapeutic Goods Administration. TGA provisionally approves two oral COVID-19 treatments, molnupiravir (LAGEVRIO) and nirmatrelvir + ritonavir (PAXLOVID) [Internet]. Available at https://www.tga.gov.au/news/media-releases/tga-provisionally-approves-two-oral-covid-19-treatments-molnupiravir-lagevrio-and-nirmatrelvir-ritonavir-paxlovid [accessed on 19 November 2022].

76. Pfizer. PAXLOVID™ [Internet]. Available at https://www.pfizer.com/products/product-detail/paxlovidtm [accessed on 20 November 2022].

77. Keating GM, Vaidya A. Sofosbuvir: first global approval. *Drugs* 2014;74:273-282.
PUBMED | CROSSREF

78. Xu HT, Colby-Germinario SP, Hassounah SA, Fogarty C, Osman N, Palanisamy N, Han Y, Oliveira M, Quan Y, Wainberg MA. Evaluation of sofosbuvir (β-D-2′-deoxy-2′-α-fluoro-2′-β-C-methyluridine) as an inhibitor of Dengue virus replication. *Sci Rep* 2017;7:6345.
PUBMED | CROSSREF

79. Bullard-Feibelman KM, Govero J, Zhu Z, Salazar V, Veselinovic M, Diamond MS, Geiss BJ. The FDA-approved drug sofosbuvir inhibits Zika virus infection. *Antiviral Res* 2017;137:134-140.
PUBMED | CROSSREF

80. Ferreira AC, Reis PA, de Freitas CS, Sacramento CQ, Villas Bôas Hoelz L, Bastos MM, Mattos M, Rocha N, Gomes de Azevedo Quintanilha I, da Silva Gouveia Pedrosa C, et al. Beyond members of the *Flaviviridae* family, sofosbuvir also inhibits chikungunya virus replication. *Antimicrob Agents Chemother* 2019;63:e01389-18.
PUBMED | CROSSREF

81. Ju J, Li X, Kumar S, Jockusch S, Chien M, Tao C, Morozova I, Kalachikov S, Kirchdoerfer RN, Russo JJ. Nucleotide analogues as inhibitors of SARS-CoV polymerase. *Pharmacol Res Perspect* 2020;8:e00674.
PUBMED | CROSSREF

82. Elfiky AA. SARS-CoV-2 RNA dependent RNA polymerase (RdRp) targeting: an *in silico* perspective. *J Biomol Struct Dyn* 2021;39:3204-3212.
PUBMED | CROSSREF

83. Jockusch S, Tao C, Li X, Chien M, Kumar S, Morozova I, Kalachikov S, Russo JJ, Ju J. Sofosbuvir terminated RNA is more resistant to SARS-CoV-2 proofreader than RNA terminated by Remdesivir. *Sci Rep* 2020;10:16577.
PUBMED | CROSSREF

84. Messina V, Nevola R, Izzi A, De Lucia Sposito P, Marrone A, Rega R, Fusco R, Lumino P, Rinaldi L, Gaglione P, et al. Efficacy and safety of the sofosbuvir/velpatasvir combination for the treatment of patients with early mild to moderate COVID-19. *Sci Rep* 2022;12:5771.
PUBMED | CROSSREF

85. Sayad B, Khodarahmi R, Najafi F, Miladi R, Mohseni Afshar Z, Mansouri F, Rahimi Z, Shirvani M, Salimi M, Vaziri S, et al. Efficacy and safety of sofosbuvir/velpatasvir versus the standard of care in adults hospitalized with COVID-19: a single-centre, randomized controlled trial. *J Antimicrob Chemother* 2021;76:2158-2167.
PUBMED | CROSSREF

86. Roozbeh F, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, Merat S, Wentzel H, Levi J, Hill A, Shamshirian A. Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. *J Antimicrob Chemother* 2021;76: 753-757.
PUBMED | CROSSREF

87. Españo E, Kim D, Kim J, Park SK, Kim JK. COVID-19 antiviral and treatment candidates: current status. *Immune Netw* 2021;21:e7.
PUBMED | CROSSREF

88. Sokhela S, Bosch B, Hill A, Simmons B, Woods J, Johnstone H, Akpomiemie G, Ellis L, Owen A, Casas CP, et al. Randomized clinical trial of nitazoxanide or sofosbuvir/daclatasvir for the prevention of SARS-CoV-2 infection. *J Antimicrob Chemother* 2022;77:2706-2712.
PUBMED | CROSSREF

89. Tobback E, Degroote S, Buysse S, Delesie L, Van Dooren L, Vanherrewege S, Barbezange C, Hutse V, Romano M, Thomas I, et al. Efficacy and safety of camostat mesylate in early COVID-19 disease in an ambulatory setting: a randomized placebo-controlled phase II trial. *Int J Infect Dis* 2022;122:628-635.
PUBMED | CROSSREF

90. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271-280.e8.
PUBMED | CROSSREF

91. Zhou Y, Vedantham P, Lu K, Agudelo J, Carrion R Jr, Nunneley JW, Barnard D, Pöhlmann S, McKerrow JH, Renslo AR, et al. Protease inhibitors targeting coronavirus and filovirus entry. *Antiviral Res* 2015;116:76-84.
PUBMED | CROSSREF

92. Sakr Y, Bensasi H, Taha A, Bauer M, Ismail K; the UAE-Jena Research Group. Camostat mesylate therapy in critically ill patients with COVID-19 pneumonia. *Intensive Care Med* 2021;47:707-709.
PUBMED | CROSSREF

93. Gunst JD, Staerke NB, Pahus MH, Kristensen LH, Bodilsen J, Lohse N, Dalgaard LS, Brønnum D, Fröbert O, Hønge B, et al. Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial. *EClinicalMedicine* 2021;35:100849.
PUBMED | CROSSREF

94. Chupp G, Spichler-Moffarah A, Søgaard OS, Esserman D, Dziura J, Danzig L, Chaurasia R, Patra KP, Salovey A, Nunez A, et al. A phase 2 randomized, double-blind, placebo-controlled trial of oral camostat mesylate for early treatment of COVID-19 outpatients showed shorter illness course and attenuation of loss of smell and taste. Preprint at https://www.medrxiv.org/content/10.1101/2022.01.28.22270035v1 (2022).
CROSSREF

95. Yamamoto M, Kiso M, Sakai-Tagawa Y, Iwatsuki-Horimoto K, Imai M, Takeda M, Kinoshita N, Ohmagari N, Gohda J, Semba K, et al. The anticoagulant nafamostat potently inhibits SARS-CoV-2 S protein-mediated fusion in a cell fusion assay system and viral infection *in vitro* in a cell-type-dependent manner. *Viruses* 2020;12:629.
PUBMED | CROSSREF

96. Hoffmann M, Schroeder S, Kleine-Weber H, Müller MA, Drosten C, Pöhlmann S. Nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. *Antimicrob Agents Chemother* 2020;64:e00754-20.
PUBMED | CROSSREF

97. Quinn TM, Gaughan EE, Bruce A, Antonelli J, O'Connor R, Li F, McNamara S, Koch O, MacKintosh C, Dockrell D, et al. Randomised controlled trial of intravenous nafamostat mesylate in COVID pneumonitis: Phase 1b/2a experimental study to investigate safety, Pharmacokinetics and Pharmacodynamics. *EBioMedicine* 2022;76:103856.
PUBMED | CROSSREF

98. Zhuravel SV, Khmelnitskiy OK, Burlaka OO, Gritsan AI, Goloshchekin BM, Kim S, Hong KY. Nafamostat in hospitalized patients with moderate to severe COVID-19 pneumonia: a randomised Phase II clinical trial. *EClinicalMedicine* 2021;41:101169.
PUBMED | CROSSREF

99. Westendorf K, Žentelis S, Wang L, Foster D, Vaillancourt P, Wiggin M, Lovett E, van der Lee R, Hendle J, Pustilnik A, et al. LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. Preprint at https://www.biorxiv.org/content/10.1101/2021.04.30.442182v6 (2022).
CROSSREF

100. Dougan M, Azizad M, Chen P, Feldman B, Frieman M, Igbinadolor A, Kumar P, Morris J, Potts J, Baracco L, et al. Bebtelovimab, alone or together with bamlanivimab and etesevimab, as a broadly neutralizing monoclonal antibody treatment for mild to moderate, ambulatory COVID-19. Preprint at https://www.medrxiv.org/content/10.1101/2022.03.10.22272100v1 (2022).
CROSSREF

101. United States Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes new monoclonal antibody for treatment of COVID-19 that retains activity against omicron variant [Internet]. Available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains [accessed on 24 November 2022].

102. Dryden-Peterson S, Kim A, Joyce MR, Johnson JA, Kim AY, Baden LR, Woolley AE. Bebtelovimab for high-risk outpatients with early COVID-19 in a large US health system. *Open Forum Infect Dis* 2022;9:ofac565.
PUBMED | CROSSREF

103. United States Food and Drug Administration. FDA updates on bebtelovimab [Internet]. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-bebtelovimab#:~:text=%5BNovember%2030%2C%202022%5D%20FDA,read%20the%20CDER%20Statement%20here [accessed on 24 November 2022].
104. United States Food and Drug Administration. Announces bebtelovimab is not currently authorized in any US region [Internet]. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-bebtelovimab-not-currently-authorized-any-us-region [accessed on 31 January 2023].
105. Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, Yuan Y, Seegobin S, Ellery A, Levinson DJ, et al. Intramuscular AZD7442 (tixagevimab-cilgavimab) for prevention of Covid-19. *N Engl J Med* 2022;386:2188-2200.
PUBMED | CROSSREF
106. Loo YM, McTamney PM, Arends RH, Abram ME, Aksyuk AA, Diallo S, Flores DJ, Kelly EJ, Ren K, Roque R, et al. The SARS-CoV-2 monoclonal antibody combination, AZD7442, is protective in nonhuman primates and has an extended half-life in humans. *Sci Transl Med* 2022;14:eabl8124.
PUBMED | CROSSREF
107. Dong J, Zost SJ, Greaney AJ, Starr TN, Dingens AS, Chen EC, Chen RE, Case JB, Sutton RE, Gilchuk P, et al. Genetic and structural basis for SARS-CoV-2 variant neutralization by a two-antibody cocktail. *Nat Microbiol* 2021;6:1233-1244.
PUBMED | CROSSREF
108. Astrazeneca. AZD7442 PROVENT phase III prophylaxis trial met primary endpoint in preventing COVID-19 [Internet]. Available at https://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html [accessed on 25 November 2022].
109. United States Food and Drug Administration. FDA releases important information about risk of COVID-19 due to certain variants not neutralized by evusheld [Internet]. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-evusheld-not-currently-authorized-emergency-use-us [accessed on 25 November 2022].
110. VanBlargan LA, Errico JM, Halfmann PJ, Zost SJ, Crowe JE Jr, Purcell LA, Kawaoka Y, Corti D, Fremont DH, Diamond MS. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. *Nat Med* 2022;28:490-495.
PUBMED | CROSSREF
111. United States Food and Drug Administration. FDA announces Evusheld is not currently authorized for emergency use in the U.S. [Internet]. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-evusheld-not-currently-authorized-emergency-use-us [accessed on 8 February 2023].
112. Hurt AC, Wheatley AK. Neutralizing antibody therapeutics for COVID-19. *Viruses* 2021;13:628.
PUBMED | CROSSREF
113. Nathan R, Shawa I, De La Torre I, Pustizzi JM, Haustrup N, Patel DR, Huhn G. A narrative review of the clinical practicalities of bamlanivimab and etesevimab antibody therapies for SARS-CoV-2. *Infect Dis Ther* 2021;10:1933-1947.
PUBMED | CROSSREF
114. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, Hebert C, Perry R, Boscia J, Heller B, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *N Engl J Med* 2021;385:1382-1392.
PUBMED | CROSSREF
115. Deeks ED. Casirivimab/imdevimab: first approval. *Drugs* 2021;81:2047-2055.
PUBMED | CROSSREF
116. Razonable RR, Pawlowski C, O'Horo JC, Arndt LL, Arndt R, Bierle DM, Borgen MD, Hanson SN, Hedin MC, Lenehan P, et al. Casirivimab-Imdevimab treatment is associated with reduced rates of hospitalization among high-risk patients with mild to moderate coronavirus disease-19. *EClinicalMedicine* 2021;40:101102.
PUBMED | CROSSREF
117. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, Musser BJ, Soo Y, Rofail D, Im J, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med* 2021;384:238-251.
PUBMED | CROSSREF
118. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2022;399:665-676.
PUBMED | CROSSREF
119. United States Food and Drug Administration. Coronavirus (COVID-19) update: FDA limits use of certain monoclonal antibodies to treat COVID-19 due to the Omicron variant [Internet]. Available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-certain-monoclonal-antibodies-treat-covid-19-due-omicron [accessed on 29 November 2022].

120. Kim C, Ryu DK, Lee J, Kim YI, Seo JM, Kim YG, Jeong JH, Kim M, Kim JI, Kim P, et al. A therapeutic neutralizing antibody targeting receptor binding domain of SARS-CoV-2 spike protein. *Nat Commun* 2021;12:288.
PUBMED | CROSSREF

121. Kim JY, Săndulescu O, Preotescu LL, Rivera-Martínez NE, Dobryanska M, Birlutiu V, Miftode EG, Gaibu N, Caliman-Sturdza O, Florescu SA, et al. A randomized clinical trial of regdanvimab in high-risk patients with mild-to-moderate coronavirus disease 2019. *Open Forum Infect Dis* 2022;9:ofac406.
PUBMED | CROSSREF

122. European Medicines Agency. Regkirona [Internet]. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/regkirona [accessed on 21 December 2022].

123. Li M, Lou F, Fan H. SARS-CoV-2 variant Omicron: currently the most complete "escapee" from neutralization by antibodies and vaccines. *Signal Transduct Target Ther* 2022;7:28.
PUBMED | CROSSREF

124. Heo YA. Sotrovimab: First Approval. *Drugs* 2022;82:477-484.
PUBMED | CROSSREF

125. Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, Sarkis E, Solis J, Zheng H, Scott N, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med* 2021;385:1941-1950.
PUBMED | CROSSREF

126. United States Food and Drug Administration. FDA updates sotrovimab emergency use authorization [Internet]. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization#:~:text=%5B2%2F25%2F2022%5D,not%20susceptible%20to%20this%20treatment [accessed on 25 November 2022].

127. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? *J Transl Med* 2020;18:164.
PUBMED | CROSSREF

128. Rubin EJ, Longo DL, Baden LR. Interleukin-6 receptor inhibition in Covid-19 - cooling the inflammatory soup. *N Engl J Med* 2021;384:1564-1565.
PUBMED | CROSSREF

129. Kang YW, Park S, Lee KJ, Moon D, Kim YM, Lee SW. Understanding the host innate immune responses against SARS-CoV-2 infection and COVID-19 pathogenesis. *Immune Netw* 2021;21:e1.
PUBMED | CROSSREF

130. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 2017;39:529-539.
PUBMED | CROSSREF

131. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science* 2020;368:473-474.
PUBMED | CROSSREF

132. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130:2620-2629.
PUBMED | CROSSREF

133. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021;384:1491-1502.
PUBMED | CROSSREF

134. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:1637-1645.
PUBMED | CROSSREF

135. Rosas IO, Diaz G, Gottlieb RL, Lobo SM, Robinson P, Hunter BD, Cavalcante AW, Overcash JS, Hanania NA, Skarbnik A, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Med* 2021;47:1258-1270.
PUBMED | CROSSREF

136. United States Food and Drug Administration. FDA roundup: December 23, 2022 [Internet]. Available at https://www.fda.gov/news-events/press-announcements/fda-roundup-december-23-2022 [accessed on 31 January 2023].

137. Sönmez HE, Demir S, Bilginer Y, Özen S. Anakinra treatment in macrophage activation syndrome: a single center experience and systemic review of literature. *Clin Rheumatol* 2018;37:3329-3335.
PUBMED | CROSSREF

138. Monteagudo LA, Boothby A, Gertner E. Continuous intravenous anakinra infusion to calm the cytokine storm in macrophage activation syndrome. *ACR Open Rheumatol* 2020;2:276-282.
PUBMED | CROSSREF

139. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Tassan Din C, Boffini N, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020;2:e325-e331.
PUBMED | CROSSREF

140. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, Sacco E, Naccache JM, Bézie Y, Laplanche S, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020;2:e393-e400.
PUBMED | CROSSREF

141. Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, Fragkou A, Rapti A, Damoulari C, Fantoni M, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med* 2021;27:1752-1760.
PUBMED | CROSSREF

142. Sobi. Emergency use authorization | Kineret [Internet]. Available at https://www.kineretrx.com/covid19-update [accessed on 3 February 2023].

143. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis* 2020;20:400-402.
PUBMED | CROSSREF

144. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Rawling M, Savory E, Stebbing J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020;395:e30-e31.
PUBMED | CROSSREF

145. Stebbing J, Krishnan V, de Bono S, Ottaviani S, Casalini G, Richardson PJ, Monteil V, Lauschke VM, Mirazimi A, Youhanna S, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. *EMBO Mol Med* 2020;12:e12697.
PUBMED | CROSSREF

146. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054-1062.
PUBMED | CROSSREF

147. Huang KJ, Su IJ, Theron M, Wu YC, Lai SK, Liu CC, Lei HY. An interferon-γ-related cytokine storm in SARS patients. *J Med Virol* 2005;75:185-194.
PUBMED | CROSSREF

148. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, Marconi VC, Ruiz-Palacios GM, Hsieh L, Kline S, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2021;384:795-807.
PUBMED | CROSSREF

149. Eli Lilly and Company. FDA approves Lilly and Incyte's OLUMIANT® (baricitinib) for the treatment of certain hospitalized patients with COVID-19 | Eli Lilly and Company [Internet]. Available at https://investor.lilly.com/news-releases/news-release-details/fda-approves-lilly-and-incytes-olumiantr-baricitinib-treatment [accessed on 25 November 2022].

150. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020;395:473-475.
PUBMED | CROSSREF

151. Nhean S, Varela ME, Nguyen YN, Juarez A, Huynh T, Udeh D, Tseng AL. COVID-19: a review of potential treatments (corticosteroids, remdesivir, tocilizumab, bamlanivimab/etesevimab, and casirivimab/imdevimab) and pharmacological considerations. *J Pharm Pract* 2021. doi: 10.1177/08971900211048139.
PUBMED | CROSSREF

152. Hafkamp FM, Mol S, Waqué I, De Jong EC. Dexamethasone, but not vitamin D or A, dampens the inflammatory neutrophil response to protect at-risk COVID-19 patients. *Immune Netw* 2022;22:e36.
PUBMED | CROSSREF

153. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020;384:693-704.
CROSSREF

154. European Medicines Agency. EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation [Internet]. Available at https://www.ema.europa.eu/en/news/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-mechanical-ventilation [accessed on 18 December 2022].

155. National Institutes of Health. Corticosteroids [Internet]. https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/corticosteroids/ [accessed on 14 December 2022].