Review

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Drug discovery to treat COVID-19 two years after its outbreak

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SUMMARY Coronavirus disease 2019 (COVID-19) has had a significant impact on human health and economic development over the past two years. Therapeutics in combination with vaccines are critical measures to fight the pandemic. The three areas of drug development are blocking the entry of SARS-CoV-2 into cells, suppressing viral replication inside cells, and regulating the immune system, and important advances have recently been made in those areas. Increasing numbers of neutralizing antibodies and small molecules that show promise have been fully approved or authorized for emergency use, resulting in decreased mortality of patients with COVID-19. The use of therapeutics will have a great impact on formulating and revising public policies to control the pandemic. The pace of lifting of restrictions and economic recovery worldwide will also accelerate in the future. Here, the drugs or agents that have attracted considerable attention and that have led to remarkable progress in the fight against COVID-19 are reviewed

Keywords COVID-19, SARS-CoV-2, vaccine, drug, pandemic

1. Introduction

Coronavirus disease 2019 (COVID-19) has been prevalent worldwide for two years, and it has had a significant impact on human health and economic development. Although vaccination is an important measure for epidemic prevention and control, the effectiveness of vaccines may diminish as SARS-CoV-2 variants continue to emerge (*1-3*). As research on and development of COVID-19 vaccines is promoted, researchers and pharmaceutical companies worldwide are endeavoring to promote the research and development of therapeutics for COVID-19 (*4-6*). Drug development is mainly focused on three strategies: blocking virus entry into cells, inhibiting viral replication, and regulating the human immune system. Here, the drugs that have attracted considerable attention and that have led to remarkable progress in the fight against COVID-19 are reviewed.

2. Drugs that block the entry of SARS-CoV-2 into cells

SARS-CoV-2 entry into cells entails attaching to the angiotensin-converting enzyme 2 (ACE2) receptor by the spike glycoprotein present on the surface of the viral envelope (*7,8*). Then, the human transmembrane protease serine 2 (TMPRSS2) and other cellular proteases such as furin facilitate the virus' entry into cells through endocytosis or direct fusion of the viral envelope with the host membrane (*9*). Neutralizing monoclonal antibodies bind the spike protein of SARS-CoV-2, thus preventing the virus from adhering to the target cell receptor ACE2 and entering the cells (*10*). Vaccines effectively prevent COVID-19 by provoking the immune system into producing antibodies. For individuals who have comorbidities and who are ineligible for vaccination or who are receiving therapies that impair their immune response to vaccination, SARS-CoV-2-neutralising monoclonal antibodies may provide immediate, passive immunity and may limit disease progression and complications.

Casirivimab and imdevimab is a cocktail of two monoclonal antibodies (also known as REGN10933 and REGN10987, respectively) that are specifically directed against the spike protein of SARS-CoV-2 to block the virus' attachment and entry into human cells (*11*). The drug was first issued an emergency use authorization (EUA) by the US Food and Drug Administration (FDA) in November 2020 and received its last EUA update on November 2021 (*12*). The authorized use of this drug is to treat mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death

(*13*). The drug is also authorized for use as post-exposure prophylaxis for COVID-19 in individuals who are 12 years of age and older weighing at least 40 kg and are at high risk for progression to severe COVID-19, including hospitalization or death (*13*). Casirivimab and imdevimab were first approved in Japan in July 2021 to treat mild to moderate COVID-19 based on a global phase III clinical study which found that casirivimab and imdevimab reduced hospitalization or death by 70% and that the two antibodies reduced symptom duration by four days in high-risk non-hospitalized patients with COVID-19, as well as a phase I clinical study that examined the safety, tolerability, and pharmacokinetics of the antibodies in Japanese (*14,15*). Casirivimab and imdevimab have also been approved for the prophylaxis and treatment of COVID-19 in the UK, European Union, and Australia thus far (*16-18*) .

Bamlanivimab and etesevimab are neutralizing monoclonal antibodies that bind to distinct epitopes within the receptor binding domain of the spike protein of SARS-CoV-2 (*19*). This antibody combination therapy received its first EUA in the US in February 2021 and was subsequently reissued a Letter of Authorization in August, September, and December 2021 (*12*). According to the most recent EUA, emergency use of the drug combination is permitted for treatment of mild to moderate COVID-19 in adults and pediatric patients, including neonates, with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death (*20*). In addition, bamlanivimab and etesevimab are also authorized for post-exposure prophylaxis for COVID-19 in adults and pediatric individuals, including neonates, who are at high risk of progression to severe COVID-19, including hospitalization or death (*20*). According to the results of a phase III study (BLAZE-1), patients markedly benefited from bamlanivimab plus etesevimab in terms of reducing the incidence of COVID-19–related hospitalization and death and accelerating the decline in the SARS-CoV-2 viral load (*21*). Another phase III study (BLAZE-2) evaluated bamlanivimab alone for prevention of COVID-19 in residents and staff of skilled nursing facilities following a confirmed reported case of SARS-CoV-2 infection at the facility (*22*). Results from that study revealed that bamlanivimab significantly reduced the incidence of COVID-19 in the prevention population compared to a placebo (8.5% *vs*. 15.2%) (*22*). Treatment of COVID-19 with bamlanivimab and etesevimab has been granted an EUA in about 15 countries around the world thus far (*23*).

Sotrovimab (also known as VIR-7831 and GSK4182136) is a monoclonal antibody designed to attach to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2, thus limiting the ability of the virus to enter the body's cells (*24*). Emergency use of this drug was originally authorized by the US FDA in May 2021, and this EUA was reissued in October and December 2021 (*12*). Sotrovimab is permitted for treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death (*25*). An interim analysis of a phase 3 trial (COMET-ICE) revealed that sotrovimab reduced the risk of hospitalization for more than 24 hours or death by 85% compared to a placebo (*24*). In December 2021, sotrovimab was approved to treat COVID-19 patients who do not require supplemental oxygen and who are at an increased risk of developing severe disease in the UK and European Union (*26-28*).

Tixagevimab and cilgavimab are two monoclonal antibodies that bind distinct epitopes of the viral spike protein receptor binding domain to interfere with the infection process (*29*). Tixagevimab and cilgavimab, administered together, were granted an EUA in the US to prevent COVID-19 in December 2021 (*12*). The authorized use of this antibody cocktail is for pre-exposure prophylaxis for COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) with weakened immunity or who cannot be fully vaccinated due to a history of severe reaction to coronavirus vaccines (*30*). Results of a phase 3 clinical study (PROVENT) indicated that tixagevimab and cilgavimab reduced the risk of developing symptomatic COVID-19 by 77% in unvaccinated adults (≥ 18 years old) without a prior SARS-CoV-2 infection (*31*).

In September 2021, the South Korean Ministry of Food and Drug Safety (MFDS) approved regdanvimab (CT-P59), a neutralizing monoclonal antibody binding to the viral spike protein receptor binding domain, to treat COVID-19 in elderly patients ≥ 50 years of age with at least one underlying condition (obesity, cardiovascular disease, chronic lung disease, diabetes, chronic kidney disease, chronic liver disease, and patients receiving immunosuppressive agents) and mild symptoms of COVID-19, and in adult patients with moderate symptoms of COVID-19 (*32,33*). Preliminary results of a phase III clinical trial, released by the developer Celltrion, indicated that regdanvimab markedly decreased the risk of hospitalization or death by 72% versus a placebo in patients with mild-to-moderate COVID-19 symptoms who were considered at high risk of progressing to severe COVID-19 up to day 28 (*33*). In November 2021, regdanvimab was approved by the European Medicines Agency (EMA) to treat COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of their disease becoming severe (*34*). Regdanvimab has received an EUA or conditional marketing authorization (CMA) in Indonesia, Brazil, Peru, and Australia for treatment of COVID-19 thus far (*32*).

In December 2021, China's National Medical

Products Administration (NMPA) approved amubarvimab (BRII-196) and romlusevimab (BRII-198) to treat mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19 (*35*). Their indication for pediatric patients (age 12-17 weighing at least 40 kg) has been conditionally approved in China (*35*). Amubarvimab and romlusevimab are non-competing SARS-CoV-2 monoclonal neutralizing antibodies that are derived from convalesced COVID-19 patients and that have been subsequently engineered to reduce the risk of antibody-dependent enhancement and to prolong their plasma half-lives for potentially more durable efficacy (*36*). The approval of amubarvimab and romlusevimab by the NMPA is based on the results of a phase 3 clinical study (ACTIV-2) which indicated that the drugs significantly reduced the risk of hospitalization or death by 80% versus a placebo in outpatients who were considered at high risk of progressing to severe COVID-19 up to day 28 (*37*). Brii BioSciences, the developer, reported that the combination of amubarvimab and romlusevimab retains activity against major SARS-CoV-2 variants of concern, including B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.429 (Epsilon), B.1.617.2 (Delta), AY.4.2 (Delta plus), C.37 (Lambda), B.1.621 (Mu), and B.1.1.529 (Omicron) in *in vitro* studies (*38*). The US FDA is currently reviewing an application for an EUA for combination therapy with amubarvimab and romlusevimab.

The neutralizing antibodies that are currently approved or authorized for clinical use are mainly used for pre- or post-exposure prophylaxis for COVID-19 or treatment of early-stage COVID-19 in non-hospitalized patients (Table 1). Results of a recent phase III trial (ACTIV-3) indicated that neither sotrovimab nor amubarvimab plus romlusevimab displayed efficacy in improving clinical outcomes among adults hospitalized with COVID-19 (*39*), suggesting the shortcomings of neutralizing antibodies and the need for drugs with different mechanisms of action against COVID-19.

3. Drugs that suppress SARS-CoV-2 replication

SARS-CoV-2 is a spherical enveloped virus containing a single strand of positive sense RNA (*7*). Once inside the cell, the viral RNA is released into the cytoplasm and acts as messenger RNA (mRNA). Utilizing host ribosomes, two open reading frames, 1a (ORF1a) and ORF1b, of the virus genome are first translated to produce the polyproteins pp1a and pp1ab, which are then auto-proteolytically cleaved by the viral proteases PLpro and Mpro/3CLpro (encoded by ORF1a) to yield 16 nonstructural proteins (NSPs) (*4*). NSP7-16 including RNA-dependent RNA polymerase (RdRp), RNA helicase, and other proteins then form an RNA replicase-transcriptase complex (RTC) that generates new RNA genomes and mRNAs for the synthesis of structural proteins such as the spike glycoprotein (S), envelope protein (E), membrane protein (M), and the nucleocapsid phosphoprotein (N) as well as components necessary to assemble the new viral particles (*4*). The proteases Mpro/3CLpro and PLpro and components of RTC such as RdRp are potential targets for drugs to suppress viral replication (*40*).

The RdRp inhibitor remdesivir and the protease inhibitor lopinavir attracted considerable attention in early 2020 (*41-43*). A number of clinical studies have been conducted to test the efficacy and safety of these agents worldwide since the outbreak of the disease, and those studies have yielded evidence both corroborating and refuting their use to treat COVID-19 (*41*). The WHO's Solidarity clinical trial, an international collaboration to identify life-saving treatments for COVID-19, suggested that neither remdesivir nor lopinavir had obvious efficacy in hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospitalization (*44*). Variations in baseline characteristics of study populations and therapeutic regimens may have influenced outcomes in different studies. Remdesivir (intravenous route) was approved in October 2020 in the US to treat COVID-19 in hospitalized adult and pediatric patients (aged ≥ 12 years and weighing ≥ 40 kg) (*45*). An EUA was also granted to remdesivir by the US FDA for treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to < 40 kg or aged < 12 years and weighing ≥ 3.5 kg (*46*). Remdesivir was approved in Japan and received a conditional marketing authorization in the European Union for treatment of COVID-19.

Molnupiravir, an orally administered form of a potent ribonucleoside analog that inhibits the replication of SARS-CoV-2, was approved in the UK on November 4, 2021 to treat patients with mild to moderate COVID-19 and at least one risk factor for developing severe illness such as obesity, older age (> 60 years), diabetes mellitus, or heart disease (*47*). On December 23, 2021, molnupiravir was authorized by the US FDA for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19, including hospitalization or death (*48*). A randomized, double-blind, placebo-controlled clinical trial (MOVe-OUT) investigated the efficacy and safety of molnupiravir in non-hospitalized adult patients with mild to moderate COVID-19 at high risk for progression to severe COVID-19 and/or hospitalization. Results indicated that the risk of hospitalization or death was significantly reduced from 9.7% in the placebo group (68/699) to 6.8% (48/709) in the molnupiravir group. A fact worth noting is that nine deaths occurred in the placebo group and one occurred in the molnupiravir group (*49*). Given that molnupiravir is most effective when taken during the early stages of infection as revealed by the clinical data, its use is recommended as soon as possible following a positive COVID-19 test and

Table 1. Drugs that are approved or authorized for emergency use to treat COVID-19

Drug/agent	Mechanism	Indications/use	Status	Developer
Casirivimab/ Imdevimab	Neutralizing antibodies binding to ACE2	Post-exposure prophylaxis for COVID-19 or treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.	Approved in Japan, the EU, the UK, and Australia; EUA in the US	Regeneron
Bamlanivimab/ Etesevimab	Neutralizing antibodies binding to ACE2	Post-exposure prophylaxis for COVID-19 or treatment of mild to moderate COVID-19 in adult and pediatric patients including neonates who are at high risk for progression to severe COVID-19, including hospitalization or death.	EUA in the US and many other countries	Eli Lilly (Eli Lilly licensed etesevimab from Junshi Biosciences)
Sotrovimab	Neutralizing antibodies binding to ACE2	Treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death.	Approved in the UK and EU; EUA in the US	GlaxoSmithKline and Vir Biotechnology
Tixagevimab/ cilgavimab	Neutralizing antibodies binding to ACE2	Pre-exposure prophylaxis for COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) with weakened immunity or who cannot be fully vaccinated due to a history of severe reaction to coronavirus vaccines.	EUA in the US	AstraZeneca
Regdanvimab	Neutralizing antibodies binding to ACE2	Treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.	Approved in S. Korea and the EU; EUA in Indonesia, Brazil, Peru, and Australia	Celltrion
Amubarvimab/ romlusevimab	Neutralizing antibodies binding to ACE2	Treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19.	Approved in China	Brii Bio
Remdesivir	Inhibiting viral replication by inhibiting RdRp	Treatment of COVID-19 in hospitalized adult and pediatric patients.	Approved in the US and Japan	Gilead
Molnupiravir	Inhibiting viral replication as ribonucleoside analog	Treatment of mild to moderate COVID-19 in patients who have at least one risk factor for developing severe illness.	Approved in the UK; EUA in the US	Merck
Nirmatrelvir/ ritonavir	Inhibiting viral replication by inhibiting the main protease (Mpro)	Treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19.	EUA in the US	Pfizer
Dexamethasone	Immunosuppression	Treatment of severe and critical COVID-19.	Recommended by the WHO, National Health Service in the UK, and NIH in the US, and endorsed by the EMA	---
Baricitinib	Immunosuppression by inhibiting JAKs	Treatment of severe COVID-19 in adults and pediatric patients 2 years of age or older.	EUA in the US	Eli Lilly
Tocilizumab	Immunosuppression by binding the IL-6 receptor	Treatment of COVID-19 in patients two years of age and older who are receiving systemic corticosteroids and who require supplemental oxygen or mechanical ventilation.	EUA in the US; provisional approval in Australia	Genentech

Abbreviations: EUA, emergency use authorization; ACE2, angiotensin-converting enzyme 2; JAKs, Janus kinases; US, The United States; UK, The United Kingdom; EU, European Union.

within five days of the onset of symptoms (*47*).

Besides molnupiravir, the US FDA also issued an EUA for nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use, for treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death (*50*). Nirmatrelvir is a SARS-CoV-2 main protease (Mpro or 3CLpro) inhibitor while ritonavir is a CYP3A inhibitor that may inhibit the CYP3A-mediated metabolism of nirmatrelvir and consequently increase nirmatrelvir plasma concentrations to levels anticipated to inhibit SARS-CoV-2 replication (*50*). Data from a phase 2/3 randomized, double blind, placebo-controlled trial (EPIC-HR) indicated that nirmatrelvir plus ritonavir reduced the proportion of patients with COVID-19-related hospitalization or death by 88% compared to a placebo in non-hospitalized adult patients who have a prespecified risk factor for progression to severe disease or who were 60 years and older, regardless of prespecified chronic conditions (*51*).

The approval or authorized emergency use of oral small molecule drugs such as molnupiravir and nirmatrelvir/ritonavir represents major progress in the fight against COVID-19. Neutralizing antibodies have several disadvantages such as costly production, stringent storage requirements, and inconvenience to use. In terms of large-scale use, small molecule oral drugs have some advantages including a high level of compliance with medication, low-cost synthesis, and less stringent storage requirements. Early intervention with oral antivirals would be more feasible for prophylaxis or treatment of COVID-19, thus preventing infection or disease progression.

4. Drugs that regulate the immune system

The immune system functions like "a double-blade sword" in the pathogenesis of COVID-19 (*52*). The innate and adaptive immune responses evoked by SARS-CoV-2 help to eliminate the virus and promote recovery (*53*). However, a hyperinflammatory syndrome induced by SARS-CoV-2 contributes to disease severity and mortality (*54*). The natural course of COVID-19 begins with an initial stage of viral replication that might be followed by a second stage in which a cytokine storm may occur, leading to severe COVID-19 (*54,55*). Thus, the optimal stage of the disease should be selected to administer immunomodulators to treat COVID-19. A dysregulated host innate immune response is regarded as a cause of the hyperinflammatory syndrome, which is characterized by elevated serum cytokines such as IL-6 and TNF-α, in patients with severe disease (*54*). Conventional anti-inflammatory drugs such as corticosteroids, novel cytokine blockades targeting specific cytokines, such as IL-6 and TNF-α or the Janus kinase (JAK) pathway, or repurposed drugs including artesunate and imatinib have been investigated in clinical studies, and some have been granted an EUA or recommended for treatment of COVID-19.

Dexamethasone is a corticosteroid used to treat a wide range of conditions because of its anti-inflammatory and immunosuppressant action (*56,57*). Dexamethasone is recommended by the WHO to treat patients with severe and critical COVID-19 but not for patients with non-severe COVID-19 (*58*). The RECOVERY study revealed that dexamethasone reduced the incidence of death for patients on invasive mechanical ventilation or receiving oxygen without invasive mechanical ventilation but not for those who received no respiratory support (*59*). Dexamethasone has also been suggested by the National Health Service in the UK and the National Institutes of Health (NIH) in the US and it has been endorsed by the European Medicines Agency (EMA) to treat severe COVID-19 (*60-62*).

Baricitinib, a drug that has been approved to treat rheumatoid arthritis by the US FDA, is an inhibitor of Janus kinases (JAKs), which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function (*63*). In December 2020, baricitinib received an EUA from the US FDA for the treatment of COVID-19, in combination with remdesivir, in hospitalized patients requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (*64*). The EUA was revised based on the results of several clinical studies, and an updated EUA was issued by the US FDA in December 2021, in which baricitinib could be used to treat hospitalized adults and pediatric patients 2 years of age or older with severe COVID-19 (*65*).

Tocilizumab, an IL-6 receptor antibody approved to treat rheumatoid arthritis and cytokine release syndrome, is another drug that is widely used to clinically treat hyperinflammation in patients with COVID-19 (*66,67*). In June 2021, tocilizumab was granted an EUA in the US for the treatment of COVID-19 in hospitalized patients aged two years of age and older who are receiving systemic corticosteroids and who require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO based on the results of clinical studies including the RECOVERY trial, the COVACTA trial, the EMPACTA trial, and the REMDACTA trial (*68*). On December 1, 2021, tocilizumab received a provisional approval in Australia for the treatment of hospitalized patients receiving systemic corticosteroids and requiring supplemental oxygen or mechanical ventilation (*69*).

Artesunate, imatinib, and infliximab are three drugs that are already used to respectively treat malaria, certain cancers, and diseases of the immune system. These three drugs are now being tested for treatment of COVID-19 in the Solidarity PLUS trial led by the WHO (*70*). Artesunate is being evaluated for its anti-inflammatory

properties in this trial at the standard dose recommended for the treatment of severe malaria. Artesunate was reported to display anti-inflammatory action by inhibiting IL-6 and TNF-α release in animal models of acute lung injury and nephritis (*71,72*). A small-scale clinical study indicated that patients might benefit from artesunate (*73*), warranting further verification in clinical trials. Imatinib was reported to protect against capillary leakage and alveolar edema caused by inflammatory stimuli (*74*). A randomized clinical trial indicated that imatinib might confer a clinical benefit in hospitalized patients with COVID-19 (*75*), but further studies are required to validate those findings. Infliximab is a TNF-α inhibitor that has displayed efficacy and safety in restricting broad spectrum inflammation, and particularly in elderly populations who are most clinically vulnerable to COVID-19. In a small-scale clinical study, infliximab was found to abrogate pathological inflammatory signaling to facilitate clinical recovery in patients with severe or critical COVID-19 (*76*). More convincing evidence should be yielded by the WHO's Solidarity clinical trial in the future.

5. Conclusion

As more drugs are approved or authorized on an emergency basis to fight COVID-19, patient mortality should decrease further in the future. New oral antivirals have attracted considerable attention around the world because early drug intervention, a principle when using antivirals, will benefit more people, and especially those at risk of progressing to severe COVID-19. Nevertheless, the data from current clinical trials are limited, and safety and efficacy need to be evaluated through long-term and wide-ranging use. In addition, mutations in SARS-CoV-2 may lead to drug resistance, which is a major challenge that we face. A combination of social distancing, vaccines, and therapeutics is necessary to fight a "tough battle" against the epidemic. The use of therapeutics should have a great impact on formulating and revising public policies to control the pandemic. The pace of lifting of restrictions and economic recovery worldwide will also accelerate in the future.

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