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REVIEW ARTICLE

Current pharmacological treatments for COVID-19: What's next?

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Since December 2019 SARS-Cov-2 was found responsible for the disease COVID-19, which has spread worldwide. No specific therapies/vaccines are yet available for the treatment of COVID-19. Drug repositioning may offer a strategy and a number of drugs have been repurposed, including lopinavir/ritonavir, remdesivir, favipiravir and tocilizumab. This paper describes the main pharmacological properties of such drugs administered to patients with COVID-19, focusing on their antiviral, immune-modulatory and/or anti-inflammatory actions. Where available, data from clinical trials involving patients with COVID-19 are reported. Preliminary clinical trials seem to support their benefit. However, such drugs in COVID-19 patients have peculiar safety profiles. Thus, adequate clinical trials are necessary for these compounds. Nevertheless, while waiting for effective preventive measures i.e. vaccines, many clinical trials on drugs belonging to different therapeutic classes are currently underway. Their results will help us in defining the best way to treat COVID-19 and reducing its symptoms and complications.

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Abbreviations: AAK1, protein kinase 1 associated with AP2; AIFA, Italian Medicine Agency; ARDS, acute respiratory distress syndrome; BEST-RCT and BEST-CP, clinical trials on bevacizumab; CamoCO-19, clinical trial on camostat mesilate; CD147, cluster of differentiation 147; ChiCTR2000030906 and NCT04283461, studies on vaccines; ChiCTR200030254, clinical trial on favipiravir; COLCORONA, clinical trial on colchicine; EMA, European Medicine Agency; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; IL-6R, IL-6 receptor; IP-10, IFN-γ-induced protein 10; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; PD-1, programmed cell death protein 1; PD-L1, programmed death–Ligand 1; RdRp, RNA-dependent RNA polymerase; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, Transmembrane Serine Protease 2; VEGF, growth factor of vascular endothelial cells; VIP, vasoactive intestinal polypeptide; WHO, World Health Organization.

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1 | INTRODUCTION

Coronaviruses are a group of single-stranded RNA viruses that are characterized by a spherical shape. These viruses can be categorized into four subfamilies: α-/β-/γ-/δ-coronaviruses. γ- and δ-coronaviruses are more inclined to infect birds, while α- and β-coronaviruses mainly infect mammals (Yin & Wunderink, 2018). Specifically, β-coronaviruses include the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), detected in Guangdong in 2002 and in Saudi Arabia in 2012 respectively. On December 2019 a novel β-coronavirus, **SARS-CoV-2**, has emerged in Wuhan (Hubei province, China), where it was found to be responsible of the new infection COVID-19 (J. Xu et al., 2020). After a rapid worldwide spread of the disease the World Health Organization (WHO) announced COVID-19 outbreak a pandemic. According to current evidence, the epidemic started with animal to human transmission (Benvenuto et al., 2020). A phylogenetic analysis has demonstrated that the new coronavirus significantly clustered with the sequence of bat SARS-like coronavirus (Benvenuto et al., 2020). It has envelopes, and the particles are round or oval with diameter from 60 to 140 nm (National Health Commission & State Administration of Traditional Chinese Medicine, 2020). As for other coronaviruses, the replication of SARS-CoV-2 starts with the attachment to the host cell through interactions between the Spike protein (S protein) and its target protein. In this phase, the virus interacts with **ACE2** enzyme, which is attached to the outer surface of the cell membrane, and a serine protease **TMPRSS2**. Once into the cell, replication and transcription phases start (Fehr & Perlman, 2015; Hoffmann et al., 2020).

The transmission among people occurs through respiratory droplets (Q. Li et al., 2020). In mild cases, SARS-Cov-2 infection can cause fever, fatigue and dry cough, while severe cases frequently cause pneumonia, respiratory and kidney failure. Apart from respiratory and flu-like symptoms, this infection may be complicated by lymphopaenia and interstitial pneumonia with high levels of pro-inflammatory cytokines, such as **IL-1, IL-2, IL-6**, granulocyte-colony stimulating factor (G-CSF), **IP-10 (C-X-C motif chemokine 10; CXCL10)** and **TNF-α**. This condition leads to the so-called cytokine storm which, in turn, can induce acute respiratory distress syndrome (ARDS), organ failure and sepsis, potentially progressing to patient's death (Guo et al., 2020). Patients with mild form of COVID-19 should be eligible for isolation and, sometimes, symptomatic treatments (mainly **paracetamol** for fever control). On the other hand, patients presenting severe pneumonia require hospitalizations and frequently access to intensive care units, where mechanical ventilation can be provided. For these patients, pharmacological treatments are strongly needed. At present, neither specific drugs nor vaccines are available for the treatment of COVID-19. Since there is no time to evaluate new drug therapies, drug repositioning may offer a strategy to efficiently control clinical course of the disease and the spread of pandemic (Kruse, 2020).

In this paper, we aim to provide an overview of treatments currently administered in patients with COVID-19, mainly focusing on antivirals and drugs with immune-modulatory and/or anti-inflammatory properties, their pharmacological features and achievement in term of patients' clinical outcomes. A close review of drugs that are currently under clinical development is provided as well. The mechanism of action, main safety concerns and drug–drug interactions of antiviral, immune-modulatory and anti-inflammatory agents currently used or under clinical development for the treatment of COVID-19 are reported in Table 1.

2 | ANTIVIRAL AGENTS

A large number of antiviral agents, many of which are used for the treatment of human immunodeficiency virus (HIV), hepatitis and flu symptoms, are currently administered off-label worldwide in patients with COVID-19 or are under clinical evaluation for the treatment of the disease. Here, we discuss the most used antivirals in terms of pharmacodynamics, potential for the treatment of COVID-19 and data from clinical studies where available. A brief analysis of antivirals less used is also presented.

The combination **lopinavir**/**ritonavir**, which is indicated with other antiretroviral medicinal products for the treatment of HIV-1, has raised increasing interest for the treatment of COVID-19. Lopinavir is a protease inhibitor with high specificity for HIV-1 and HIV-2, while ritonavir increases lopinavir plasma concentration through the inhibition of **cytochrome P450** (Soliman, 2011). This combination was already tested in patients with SARS infection, demonstrating to be associated with favourable outcomes, and it is currently evaluated, in combination with **IFN-β**, in patients with MERS-CoV infection (Arabi et al., 2018; Arabi et al., 2020; Dayer, Taleb-Gassabi, & Dayer, 2017). Cao et al. carried out a randomized, controlled, open-label trial in 199 hospitalized patients with severe SARS-CoV-2 infection. Patients were randomized to receive the combination lopinavir/ritonavir plus standard care for 14 days or standard care alone. According to study's results, no differences between the combination treatment and the standard treatment, in terms of clinical improvement, mortality at 28 days and the percentages of patients with detectable viral RNA could be demonstrated Moreover, adverse events, especially gastrointestinal ones, were more common in the group of patients receiving the combination treatment, while serious adverse events were more common in the standard-care group. Authors concluded that in hospitalized patients with severe COVID-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care (Cao et al., 2020). Furthermore, an open-label, randomized clinical trial, which will compare the efficacy of lopinavir/ritonavir versus **hydroxychloroquine** in

TABLE 1 Mechanism of action, main safety concerns and potential drug–drug interactions of antiviral, immune-modulatory and anti-inflammatory agents currently used or under clinical development for the treatment of COVID-19

Therapeutic class	Drug(s)	Main mechanism of action	Common adverse events	Drug–drug interactions	Ref.
Antivirals	*Lopinavir/ritonavir*	HIV protease inhibitor/CYP450 inhibitor	Gastrointestinal adverse events (nausea, vomiting and and diarrhoea)	CYP3A inhibitors, tadalafil, riociguat, vorapaxar, fusidic acid, salmeterol and rivaroxaban	Soliman, 2011; The EMA b, 2020
	Remdesivir	RNA-dependent RNA polymerase inhibitor	Hepatic adverse events	The risk of drug–drug interactions is limited by remdesivir rapid clearance	Sheahan et al., 2020; The EMA c, 2020
	Favipiravir	RNA-dependent RNA polymerase inhibitor	Abnormal liver function test, psychiatric and gastrointestinal adverse events, increase in serum uric acid	NA	Furuta, Komeno, and Nakamura, 2017
	Darunavir/cobicistat	HIV protease inhibitor/CYP450 inhibitor	Gastrointestinal adverse events (nausea, vomiting and diarrhoea), headache	Colchicine and strong inhibitors of CYP3A and P-glycoprotein	Deeks, 2018; The EMA d, 2020
	Camostat mesilate/ nafamostat	Serine protease inhibitors	Skin rashes, itching, gastrointestinal adverse events (nausea, diarrhoea and abdominal pain) and changes in liver enzymes	NA	Zhou et al., 2015
Immuno-modulatory and anti-inflammatory drugs	*Tocilizumab*	IL-6R inhibitor	Infections, headache, hypertension and increase in hepatic enzymes	Drugs metabolized by CYP3A4, 1A2 or 2C9	Scott, 2017
	Chloroquine/ Hydroxychloroquine	Interferences with terminal glycosylation of ACE2 receptor	Cardiovascular disorders, including prolongation of QT	Digoxin, class IA and III antiarrhythmic, tricyclic antidepressants, antipsychotics	Agenzia Italiana del Farmaco d, 2019; Dong et al., 2020
	Colchicine	Inhibition of the metabolism and chemotaxis of polymorphonuclear cells	Diarrhoea, gastrointestinal bleeding, skin rashes, kidney and liver damage	CYP3A4 and P-glycoprotein inhibitors	Agenzia Italiana del Farmaco e, 2020; Gao et al., 2020
	Baricitinib	JAK1 and JAK2 inhibitor	Increased LDL cholesterol, upper respiratory tract infections and nausea	OAT3 inhibitors	Agenzia Italiana del Farmaco c, 2020
	Aviptadil	Vasoactive intestinal polypeptide (VIP) analogue	NA	NA	Li et al., 1996
	Eculizumab	Inhibitor of the terminal complement system	Headache, infections, leukopenia, anaemia, gastrointestinal adverse events and flu-like symptoms	Rituximab and chronic intravenous human immunoglobulin	The EMA , 2020

Abbreviation: NA, not available.

150 patients with mild COVID-19, is currently ongoing in the Republic of Korea (Clinicaltrial.gov a, 2020). Since clinical evidence on the efficacy and safety of the combination lopinavir/ritonavir in patients with COVID-19 is still limited and controversial, further studies are required to confirm a possible role of these drugs. Nevertheless, this combination is currently used in Italy in COVID-19 patients with less disease severity compared with patients evaluated in the study published on NEJM (Cao et al., 2020; Agenzia Italiana del Farmaco a, 2020)

Remdesivir has been recently recognized as a promising antiviral drug against a broad spectrum of RNA viruses (including MERS-CoV) infection in cultured cells (Sheahan et al., 2020), mice and non-human primate models (De Wit et al., 2020). It is a nucleotide analogue, able to inhibit RNA-dependent RNA polymerase (RdRp), proteins essential for viral replication. The drug was initially developed as a treatment for Ebola and Marburg infections but did not demonstrate clinical efficacy. However, antiviral activities were also demonstrated against single-stranded RNA viruses, including MERS and SARS-Cov (Agostini et al., 2018). Recent results from a preclinical study indicated that, *in vitro*, the association remdesivir/**chloroquine** could be highly effective in controlling the SARS-Cov-2 infection (M. Wang et al., 2020). The efficacy and safety of remdesivir are currently being evaluated in a phase 3 clinical trial in 237 patients with COVID-19, which ended on April 10, 2020 (Clinicaltrial.gov b, 2020). In addition, a further phase 3 trial is evaluating the efficacy and safety of remdesivir in 1,600 patients with COVID-19; this study will end in May 2020 (Clinicaltrial.gov c, 2020). Data from the Italian real clinical practice showed that the drug has already been used in patients with COVID-19 at the Spallanzani hospital in Rome and that it is currently being administered in 12 Italian clinical centres (Adnkronos, 2020). Lastly, a case report highlighted promising results for this treatment in the first US patient with COVID-19 (Holshue et al., 2020).

Favipiravir is another drug under clinical development. It was authorized in 2014 in Japan for the treatment of influenza virus infections. The drug is converted by intracellular phosphoribosylation into its active form that selectively inhibits RNA-dependent RNA polymerase (RdRp). Since the catalytic domain of RdRp is expressed in many types of RNA viruses, favipiravir is effective against a wide range of influenza virus subtypes but also against arenavirus, bunyavirus and filovirus (Furuta, 2017). Favipiravir has already been used for the treatment of patients with Ebola and Lassa viruses. However, no clear conclusions about the efficacy profile of the drug were drawn (Delang, Abdelnabi, & Neyts, 2018). As reported by Watanabe (2020), favipiravir was administered during a clinical trial to 200 patients with COVID-19 at hospitals in Wuhan and Shenzhen. The results of these studies showed that patients who received the drug tested negative in a relatively short time (4 days compared to 11 days in the control group), while the symptoms of pneumonia were significantly reduced. No specific safety concerns have emerged. Another clinical study carried out in Wuhan showed that favipiravir-treated patients recovered from fever after an average of 2.5 days compared to 4.2 days in other patients. Chang Chen et al. (2020) recently published the results of a randomized clinical trial (Chictr.org.cn, n. ChiCTR200030254), which compared the efficacy and safety of favipiravir versus umifenovir in the treatment of 240 patients with COVID-19, hospitalized in three hospitals from February 20, 2020, to March 12, 2020. These results showed that the 7-day clinical recovery rate was 55.86% in the umifenovir group and 71.43% in the favipiravir group ($P = 0.01$). In patients with hypertension and/or diabetes, the time for fever reduction and cough relief was significantly shorter in favipiravir group than in umifenovir group ($P < 0.001$), but no statistically significant difference regarding oxygen therapy or non-invasive mechanical ventilation was found. The most common adverse events were liver enzyme abnormalities, psychiatric, gastrointestinal symptoms and serum uric acid elevations (2.5% of patients in the umifenovir group vs. 13.79% of patients in the favipiravir group, $P < 0.0001$). Lastly, the drug is under evaluation for the treatment of COVID-19 in a 3-arms, multicentre randomized controlled trial in combination with tocilizumab (Clinicaltrial.gov d, 2020). At the end of March 2020, the Italian Medicine Agency (AIFA) started the evaluation of available scientific evidences with the aim to understand if a clinical programme to assess the efficacy and safety of favipiravir is appropriate (Agenzia Italiana del Farmaco b, 2020).

Another group of antiviral agents are also being considered as potential treatments for SARS-Cov-2 infection. For these antivirals, a brief description is reported below. Among these, there is the combination darunavir/**cobicistat**, which is currently approved for the treatment of HIV-1 in association with other antivirals. Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease, while cobicistat is an inhibitor of cytochromes P450 that enhances darunavir plasma concentrations (Deeks, 2018). Based on the results of preclinical studies, which demonstrated inhibitory effects of this combination on SARS-CoV-2 (Lin, Shen, He, Li, & Guo, 2020; Omotuyi et al., 2020), these drugs are currently being evaluated in some clinical studies (Clinicaltrial.gov e, 2020; Clinicaltrial.gov f, 2020). Lastly, an analysis by Jeffrey K. Aronson of clinical trials on COVID-19 revealed that there were currently more than 20 studies investigating the efficacy of other antivirals, including triazavirin (non-nucleoside antiviral drug, effective against tick-borne encephalitis virus and forest-spring encephalitis virus), azidovudine (azidothymidine nucleoside analogue, inhibitor of HIV reverse transcriptase), umifenovir (membrane haemagglutinin fusion inhibitor in influenza viruses), danoprevir (Hepatitis C virus NS3 protease inhibitor) and baloxavir marboxil (inhibitor of influenza virus cap-dependent endonuclease) (CEBM, 2020). **Sofosbuvir**, galidesivir and tenofovir showed promising results for use against the newly emerged strain of coronavirus (Elfiky, 2020). Other antivirals, such as oseltamivir, peramivir, zanamivir, ganciclovir, **acyclovir** and **ribavirin**, which are commonly used in clinical practice, are currently not recommended for COVID-19 (Guo et al., 2020). Even though there have been a few reports of the use of some of these drugs in patients with COVID-19, researchers highlighted the importance to not give patients drugs of unknown efficacy, which might be very harmful for those with severe COVID-19 (D. Wang et al., 2020).

Recently, two other drugs are currently evaluated in patients with COVID-19, **camostat mesilate** and **nafamostat**. These drugs are synthetic protease inhibitors of trypsin, prostasin, matriptase and plasma kallikrein. They are approved in Japan for the treatment of chronic pancreatitis and post-operative reflux esophagitis. Coronaviruses penetrate the cell through the plasma membrane; this step requires the activation of superficial proteases, such as TMPRSS2. Specifically, SARS-CoV-2 enters human cells after that the S protein binds to the ACE2 enzyme on the cell membrane. S protein is divided into S1 and S2 by a protease derived from human cells. S1 binds to its target, ACE2. The S2 is divided by TMPRSS2, with consequent fusion of the membrane. ACE2 and TMPRSS2 are therefore essential for SARS-CoV-2 infection. Both these drugs are able to inhibit the enzymatic activity of TMPRSS2 (Hoffmann et al., 2020; Zhou et al., 2015). A randomized, placebo-controlled clinical trial (CamoCO-19) is evaluating the efficacy and safety of camostat mesilate in 180 patients with COVID-19 (Clinicaltrial.gov g, 2020). Furthermore, both drugs will also be evaluated in clinical trials launched by the University of Tokyo (Institute Of Medical Science, The University Of Tokyo, 2020). Camostat seems well tolerated with common adverse events which include rashes, gastrointestinal disorders and changes in liver enzymes. Rare adverse events are thrombocytopenia, liver failure and hyperkalaemia. Camostat mesilate was associated with a case of acute eosinophilic pneumonia (Ota et al., 2016). Another glycoprotein involved in the passage of the virus inside the cell is cluster of differentiation 147 (CD147), which interacts with S protein. CD147 also shows pro-inflammatory activity and takes part in the regulation of cytokine secretion and in leukocytes chemotaxis during viral infections (Bian et al., 2020). Chinese researchers have started a clinical trial to test the efficacy and safety of meplazumab, a monoclonal antibody that binds the CD147 glycoprotein. Even though this drug cannot be defined as an antiviral agent, its mechanism of action leads to a control in virus replication, for this reason it is mentioned among antivirals. The preliminary results of the Chinese study are promising. Indeed, compared to the control group, the treatment with meplazumab was earlier associated with improvement in pneumonia. These results, although preliminary, seem to confirm the involvement of CD147 in the penetration and replication of the virus in the body as well as in the development of inflammatory processes related to the infection (Clinicaltrial.gov h, 2020).

Lastly, a recent study carried out by the Monash University's Biomedicine Discovery Institute and the Peter Doherty Institute of Infection and Immunity showed that **ivermectin**, a medication used for the treatment of parasite infestations, in cell culture is able to reduce the viral RNA of SARS-Cov-2 by 93% after 24 h and by 99.8% after 48 h. Currently, tests were carried out only *in vitro* and clinical trials are strongly needed to evaluate if the drug can be really effective against SARS-Cov-2. The author concluded that the early administration of an effective anti-viral to patients could limit their viral load, contrast the disease progressing and prevent its transmission. They suggest that ivermectin could be a useful antiviral in the fight against COVID-19 (Caly, Druce, Catton, Jans, & Wagstaff, 2020).

3 | IMMUNOMODULATORY AND ANTI-INFLAMMATORY AGENTS

As previously reported, the SARS-Cov-2 infection can be associated, especially in severe form, with the exaggerate activation of inflammatory processes and the development of cytokine storm. Based on this consideration, several drugs with immunomodulatory properties are currently evaluated in patients with COVID-19. These drugs include both synthetic and biological medicines that are able to modulate specific inflammatory pathways through the inhibition of human IL-6 receptor (**IL-6R**), of the metabolism, motility and chemotaxis of polymorphonuclear cells, of JAK or TNF-α production.

One of the first drugs used in patients with COVID-19 was **tocilizumab**. This is a monoclonal antibody that inhibits ligand binding to the IL-6R and that is authorized for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis (Scott, 2017). Scientific evidence suggests that the IL-6 pathway plays a key role in guiding the inflammatory immune response at the level of pulmonary alveoli in patients affected by COVID-19. Indeed, this immune response produces damage to the lung parenchyma, which significantly reduces respiratory function (Mehta, 2020; Zhang et al., 2020). The drug was first tested in China to reduce lung complications in 20 patients with severe SARS-CoV-2 infection (X. Xu et al., 2020). The treatment was associated with a reduction of oxygen requirement, resolution of CT lesions, normalization of lymphocyte count, reduction of C-reactive protein levels and hospital discharge, with average hospitalization duration of 13.5 days. Given the achieved clinical outcomes, the drug is currently used in several Italian hospitals, including the Cotugno Hospital in Naples. Since tocilizumab seems able to prevent the hyperactivation of inflammatory pathway, its use can be expected also in early stages for patients with not severe COVID-19. Currently, three clinical studies, including one that was authorized by the AIFA, are ongoing (Clinicaltrial.gov i, 2020; Clinicaltrial.gov l, 2020). **Sarilumab** belongs to the same drug class of tocilizumab, and three trials are underway to evaluate the efficacy and safety of this drug, alone or in combination with standard care, in almost 1,500 patients with COVID-19 (Clinicaltrial.gov m, 2020; Clinicaltrial.gov n, 2020; Clinicaltrial.gov o, 2020).

Two other drugs, chloroquine and hydroxychloroquine, are off-label used in Chinese and Italian clinical centres for the treatment of COVID-19 (Dong, Hu, & Gao, 2020), and they were labelled as "miracle cure" in the USA (The Guardian, 2020). These compounds are authorized as antimalarial drugs and for the treatment of autoimmune diseases, including lupus and rheumatoid arthritis. Even though both drugs are considered to be safe with adverse events that are generally mild and transitory, they can be associated with cardiovascular disorders, including prolongation of QT that can be life-threatening (Frisk-Holmberg, Bergqvist, & Englund, 1983). They may also induce retinal toxicity that was described with long-term use (Easterbrook, 1993; Mavrikakis, Papazoglou, Sfikakis, Vaiopoulos, & Rougas, 1996). Furthermore, since the incidence of hepatic abnormalities significantly increases in patients with COVID-19, an impaired metabolism of both medications can be expected, leading to further increase in the risk of

liver impairment (Rismanbaf & Zarei, 2020). Some preclinical studies showed that chloroquine has antiviral activity against SARS coronavirus (Keyaerts, Vijgen, Maes, Neyts, & Ranst, 2004), human coronavirus OC43 (Keyaerts et al., 2009) and influenza A H5N1 (Yan et al., 2013), suggesting a possible role in SARS-Cov-2 infection (Gao, Tian, & Yang, 2020; Inglot, 1969). Further studies found that chloroquine interferes with terminal glycosylation of the functional ACE2 enzyme, negatively influencing the virus-receptor binding. Indeed, results of a clinical study showed that the combination remdesivir/chloroquine or hydroxychloroquine is highly effective in control of SARS-Cov-2 infection (Colson, Rolain, Lagier, Brouqui, & Raoult, 2020; Vincent et al., 2005). Both drugs are currently used in Italy in patients with SARS-Cov-2 infections, including outpatients in early stages of disease, and, given their particular safety profile, the AIFA recommended to healthcare professionals to perform a careful evaluation of these patients, particularly in cases of cardiac conduction disorders, glucose-6-phosphate dehydrogenase deficiency or the presence of other concomitant therapies (Agenzia Italiana del Farmaco c, 2020). Data from a recent systematic review of six scientific articles and 23 ongoing clinical trials showed that chloroquine seems to be effective in reducing SARS-CoV-2 replication in vitro. However, authors underlined that even though a rationale to justify clinical research on chloroquine in patients with COVID-19 exists, high-quality clinical trials are urgently needed in order to confirm a favourable efficacy and safety profile (Cortegiani, Ingoglia, Ippolito, Giarratano, & Einav, 2020). On the other hand, a further literature review (Gbinigie & Frie, 2020) showed that there is limited evidence of *in vitro* activity of both drugs against SARS-CoV-2, while clinical data was derived from only two studies (J. Chen et al., 2020; Gautret et al., 2020) with small sample size (overall, 66 patients) and methodological limitations, with no data on medium or long-term follow-up. In conclusion, currently scientific evidence on the efficacy and safety of chloroquine and hydroxychloroquine in patients with COVID-19 are scarce. High-quality randomized clinical trials are strongly needed. Another drug able to reduce the cytokine storm is colchicine that is authorized for the treatment of acute attack of gouty arthritis and pericarditis. The drug reduces the inflammatory response through several mechanisms:- the inhibition of the metabolism, motility and chemotaxis of polymorphonuclear cells, the inhibition of the adhesion and recruitment of neutrophils and the modulation of leukocyte-mediated inflammatory activities (Andreu & Timasheff, 1982; Chia, Grainger, & Harper, 2009; Dalbeth & Lauterio, 2014; Z. Li, Davis, Mohr, Nain, & Gemsa, 1996; Martinon, Pétrilli, Mayor, Tardivel, & Tschopp, 2006). On March 2020, a phase 3 clinical study (COLCORONA) began. This study will enrol 6,000 outpatients with COVID-19 with the following characteristics:- age ≥ 40 years; diagnosis of COVID-19 in the past 24 h; at least one risk factor between age > 70 years, diabetes, uncontrolled hypertension, asthma or COPD, heart failure, fever ≥38.4° C in the last 48 h, dyspnoea, pancytopenia or high neutrophil count and low lymphocyte count and finally patients not of childbearing age or using contraception methods (Clinicaltrial.gov p, 2020).

Baricitinib is currently approved for the treatment of rheumatoid arthritis. It is a selective and reversible inhibitor of **JAK1** and **JAK2**. These enzymes transduce intracellular signals for cytokines and growth factors involved in haematopoiesis, inflammation and immune function. Furthermore, baricitinib blocks the protein kinase 1 associated with AP2 (**AAK1**), preventing the binding of the virus to the alveolar epithelium (Mayence & Vanden Eynde, 2019). A study published in The Lancet suggested that this drug could represent an additional therapeutic alternative for the treatment of COVID-19 (Richardson et al., 2020). A non-randomized phase II clinical trial was recently started in order to evaluate the efficacy and safety of baricitinib, lopinavir/ritonavir, hydroxychloroquine and sarilumab in the treatment of 1,000 hospitalized patients with COVID-19. Similarly, **sunitinib**, **fedratinib** and **ruxolitinib**, which are all selective JAK inhibitors, may be potentially effective against SARS-CoV-2 in reducing inflammation and cytokine levels, including IFN-γ and IL-6, and virus endocytosis (Clinicaltrial.gov q, 2020; Stebbing et al., 2020; Favalli et al., 2020; Bekerman et al., 2017).

Aviptadil is an analogue of vasoactive intestinal polypeptide (VIP). This drug is authorized for the treatment of erectile dysfunction, sarcoidosis and acute lung damage. The rationale for its use for the treatment of ARDS is based on the results from preclinical studies showing that the VIP is highly concentrated in the lung, where it prevents the activation of **caspases NMDA**-induced, inhibits IL-6 and TNF-α production and protects against HCl-induced pulmonary oedema (Leuchte et al., 2008; Petkov et al., 2003; Said, 2012). In a clinical study, 7/8 patients with severe ARDS were successfully treated with ascending doses of the VIP (Clinicaltrial.gov r, 2020). A phase II clinical trial based on patients with COVID-19 infection will begin shortly.

Eculizumab is a monoclonal antibody approved for the treatment of atypical haemolytic uraemic syndrome, refractory generalized myasthenia gravis and neuromyelitis spectrum disorders. It is an inhibitor of the terminal portion of the complement cascade involved in the inflammatory response. Even though the role of complement cascade in the pathogenesis of SARS-CoV-2 infections is uncertain, many studies suggested that its inhibition might potentially work as a therapeutic approach (Gralinski et al., 2018; Ip et al., 2005; Yuan et al., 2005). Based on these considerations, eculizumab will be tested in the SOLID-C19 clinical trial in the treatment of patients with severe SARS-CoV-2 and ARDS (Clinicaltrial.gov s, 2020). A phase 2/3 randomized, open-label, study is investigating the efficacy and safety of **emapalumab**, a monoclonal antibody targeting IFN-γ, and **anakinra**, an antagonist of **IL-1R**, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection (Clinicaltrial.gov t, 2020). This study received the approval by the AIFA (Ministero della Salute, 2020).

Finally, noteworthy is the use of corticosteroids. A recent document released by the WHO specified that these drugs are adjunctive therapies for COVID-19. Specifically, it has been reported that, according to the results of a systematic review of observational studies, the use of corticosteroids in patients with SARS was not associated with survival benefit (Stockman, Bellamy, & Garner, 2006). Similarly, a further systematic review of observational studies found a higher risk of mortality and secondary infections with

corticosteroids administered in patients with flu (Rodrigo, Leonardi-Bee, Nguyen-Van-Tam, & Lim, 2016). However, this effect was not confirmed by a subsequent study (Delaney, 2016). Therefore, the WHO recommend for patients with COVID-19 to use corticosteroids only if they are indicated for another reason such as exacerbation of asthma or COPD, septic shock (WHO a, 2020). Literature data support that corticosteroids do not add clinical benefits in the treatment of COVID-19 infection (Ling et al., 2020). On the other hand, some studies reported improvements in SARS patients treated with **methylprednisolone**, also in terms of reduction of IL-8, monocyte chemo-attractant protein-1 and Th1 chemokine IFN-γ-inducible protein-10 (CXCL10; Sung et al., 2004; Wong et al., 2004), while one case reports described positive effects of methylprednisolone on clinical outcomes of one patient with COVID-19 (L. Zhu et al., 2020). In conclusion, considering that evidence available is quite conflicting regarding to corticosteroids in patients with COVID-19, their use should undergo a case-by-case evaluation.

4 | OTHER THERAPIES AND FUTURE PERSPECTIVES

Many other drugs with disparate mechanisms of actions are evaluated in patients with COVID-19. For instance, a PD-1 immune checkpoint inhibitor monoclonal antibody, **camrelizumab**, which recently received a conditional approval in China for the treatment of relapsed or refractory classical Hodgkin lymphoma, is evaluated in a phase 2 study involving patients with SARS-Cov-2 infection. **PD-1** and its ligand (**PD-L1**) are key mediators in T cell depletion in patients with sepsis. Preclinical studies have demonstrated that the blockade of PD-1 or PD-L1 can prevent T cell death, regulate cytokine production and reduce organ dysfunction (Markham & Keam, 2019; X. D. Zhu & Sun, 2019). The study was launched on February 2020 to verify its efficacy in combination with thymosin in 120 patients with severe pneumonia associated with lymphocytopenia (Clinicaltrial.gov u, 2020). A further experimental monoclonal antibody for the treatment of COVID-19 is **bevacizumab**, approved for the treatment of metastatic colorectal cancer, non-small cell lung cancer, metastatic breast cancer and advanced and/or metastatic renal cell carcinoma. By binding to the growth factor of vascular endothelial cells (**VEGF**), a key promoter of vasculogenesis and angiogenesis, bevacizumab is able to prevent its biological activity (US FDA, 2008, European Medicine Agency [EMA a], 2008). A key role of VEGF in acute lung injury and ARDS was confirmed (Barratt, Medford, & Millar, 2014). Based on these findings, two clinical trials are currently evaluating the efficacy and safety of bevacizumab in patients with COVID-19 (BEST-RCT and BEST-CP) (Clinicaltrial.gov v, 2020; Clinicaltrial.gov z, 2020). Also for **thalidomide**, a drug widely used in the treatment of Interstitial Pulmonary Fibrosis, lung damage from **paraquat** and myeloma, a possible role for the treatment of COVID-19 was hypothesized. Indeed, the drug has been reported to be effective against HIV (Kwon, Han, Im, Baek, & Lee, 2019; Moreira et al., 1997) by modulating TNF-α-induced replication. Moreover, thalidomide suppresses the production of proinflammatory cytokines such as TNF-α and IL-8 through the inhibition of NF-κB (Mazzoccoli et al., 2012). Two studies are currently testing its efficacy in patients with COVID19 (Clinicaltrial.gov aa, 2020; Clinicaltrial.gov ab, 2020).

In addition, other drugs are currently evaluated in Chinese clinical trials involving patients with COVID-19, including **fingolimod** (Smart patients, 2020), high-dose **vitamin C**, **adalimumab**, **piperaquine** and **leflunomide** (Chinese Clinical Trial Register, 2020). Lastly, considering the key role of ACE2 for the attachment and cell entry of SARS-Cov-2, researchers recently suggested that the development of specific neutralizing monoclonal antibodies that bind to ACE2 might block the virus entry (Shanmugaraj, Siriwattananon, Wangkanont, & Phoolcharoen, 2020).

Lastly, given that the therapy for COVID-19 is dependent on the patients' immune system, researchers are evaluating two possible engineering therapies, expanded umbilical cord mesenchymal stem cells in critically ill patients (Atluri, Manchikanti, & Hirsch, 2020) and intravenous immunoglobulin purified from IgG antibodies of patients who recovered from COVID-19 (Jawhara, 2020). In addition, human convalescent serum may represent a good option for the prevention and treatment of COVID-19 (Hopkins, 2020). Despite high expectations for convalescent serum, related risks should be considered, including those associated with inadvertent infection, immunological reactions, the development of antibody-dependent enhancement of infection and the attenuation of the immune response that may be responsible for vulnerability to subsequent reinfection (Casadevall & Pirofski, 2020). Finally, the development of a vaccine against SARS-CoV-2 is urgently needed. However, according to Shang, Yang, Rao, and Rao (2020), researchers would bring a new SARS-CoV-2-based vaccine in approximately 16–20 weeks. On March 2020, there were two candidate vaccines in phase 1 development (studies ChiCTR2000030906 and NCT04283461) and 42 candidate vaccines in preclinical phase of evaluation (WHO b, 2020). Researchers from the University of Pittsburgh School of Medicine announced a potential vaccine against SARS-CoV-2 that was tested in mice and produced antibodies specific to SARS-CoV-2 able to neutralize the virus (Science Daily, 2020). Furthermore, an experimental mRNA vaccine against the pandemic coronavirus was already administered to one person in the United States (Cohen, 2020).

5 | CONCLUSION

Since the beginning of the outbreak, a large number of clinical studies have been registered worldwide, and several drugs were repurposed to face the new health emergency of COVID-19. We described pharmacological properties and available clinical data for several drugs, mainly antiviral, immune-modulatory and anti-inflammatory agents. For many of these drugs, including lopinavir/ritonavir, remdesivir, favipiravir and tocilizumab, evidence from preliminary clinical trials seems to support their benefit in improving patients' clinical conditions. However, considering that adequate clinical trials are necessary

to reach any firm conclusion on the efficacy profiles of these compounds, we believe that their use should be restricted to controlled environments and under adequate clinical studies.

Considering that nowadays, no specific treatments are available for COVID-19, drugs repurposing is necessary, but it requires caution. Indeed, too many drugs that are currently tested in patients with COVID-19 have an unknown efficacy profile. On the other hand, those with proven efficacy have a peculiar safety profile, which calls for a strict monitoring of treated patients. Therefore, patients treated with such drugs should undergo a routine monitoring. Furthermore, as reported by The Liverpool Drug Interaction Group, particular attention should be given at adverse events deriving from drug–drug interactions, which could be very common in patients with COVID-19, given the huge amount of pharmacological therapies to which they are subjected to (The Liverpool Drug Interaction Group, 2020).

Worldwide regulatory agencies are promoting many interventions to guarantee access to effective and safe medicines, though no proven specific therapies are available to prevent or treat COVID-19. In addition, on March 18, the EMA and the US FDA jointly chaired the first global regulatory meeting experts to support proceeding to first-in-human clinical studies (H. Chen et al., 2020). Since SARS-Cov-2 is still an unknown virus, we are now learning its transmission mechanisms, clinical spectrum of disease, diagnostics and lethality. In conclusion, while waiting for the development of an effective vaccine, many clinical trials on different types of drugs are currently underway. Their results will certainly bring new knowledge and will help us in defining the best way to treat COVID-19 and reducing its symptoms and complications.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018) are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Kelly, et al., 2019; Alexander, Christopoulos, et al., 2019).

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CONLICT OF INTEREST

The authors declare no conflicts of interest.

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