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

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Abstract

Starting from December 2019 the novel SARS-Cov-2 has spread all over the world, being recognized as the causing agent of COVID-19. Since nowadays no specific drug therapies neither vaccines are available for the treatment of COVID-19, drug repositioning may offer a strategy to efficiently control the clinical course of the disease and the spread of the outbreak. In this paper we aim to describe the main pharmacological properties, including data on mechanism of action, safety concerns and drug-drug interactions, of drugs currently administered in patients with COVID-19, focusing on antivirals and drugs with immune-modulatory and/or anti-inflammatory properties. Where available, data from clinical trials involving patients with COVID-19 were reported. A large number of clinical studies have been registered worldwide and several drugs were repurposed to face the new health emergency of COVID-19. For many of these drugs, including lopinavir/ritonavir, remdesivir, favipiravir, chloroquine and tocilizumab, clinical evidence from literature and real life settings support their favorable efficacy and safety profile in improving patients' clinical conditions. Even though drug repurposing is necessary, it requires caution. Indeed, too many drugs that are currently tested in patients with COVID-19 have peculiar safety profiles. While waiting for the results of clinical studies demonstrating the efficacy of drugs able to reduce symptoms and complications of COVID-19, the best therapeutic path to pursue is the development of an effective vaccine able to prevent this infection.

1. Introduction

Coronaviruses are a group of single-stranded RNA viruses that are characterized by a spherical shape, which provides them the typical "crown" appearance. These viruses, which were first identified in the mid-1960s, can be categorized into four subfamilies: α-/b-/g-/d-Coronavirus. Gamma and delta-coronaviruses are more inclined to infect birds, while alpha and beta-coronaviruses mainly infect mammals [**1**]. 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 (*Severe Acute Respiratory Syndrome Coronavirus 2*), has emerged in Wuhan (Hubei province, China) where it was found to be responsible of the new COVID-19 [**2**]. After a rapid spread worldwide 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 [**3**]. A phylogenetic analysis has demonstrated that the new coronavirus significantly clustered with the sequence of bat SARS-like coronavirus [**3**]. It has envelopes, and the particles are round or oval with diameter from 60 to 140 nm [**4**]. 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 receptor. In this phase, the virus interacts with ACE2 receptor and the serine protease TMPRSS2. Once into the cell, replication and transcription phases start [**5,6**].

The transmission among people occurs through respiratory droplets ad the incubation time ranges from 3 days to 2 weeks [**7**]. In mild cases SARS-Cov-2 infection can occur with fever, fatigue and dry cough, while severe cases frequently occur with pneumonia, respiratory and kidney failure. Apart from respiratory and flu-like symptoms, this infection may be complicated by lymphopenia and interstitial pneumonia with high levels of pro-inflammatory cytokines, such as IL-1, IL-2, IL-6, G-CSF, IP-10, and TNFα. This condition leads to the so-called "cytokine storm" which, in turn, can induce acute respiratory distress syndrome (ARDS), organ failure, sepsis, potentially progressing to patient's death [**8**]. Patients with mild form of COVID-19 shall 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 the access to intensive care units where mechanical ventilation can be provided. For these patients pharmacological treatments is strongly needed. Nowadays, no specific drug therapies neither 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 [**9**].

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 examination 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 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 pharmacodynamic properties, potential for the treatment of COVID-19 and data from clinical studies where available. A brief analysis of antivirals less used is presented as well.

The combination lopinavir/ritonavir, which is indicated with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1), have 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 [**10**]. This combination was already tested in patients with SARS infection, demonstrating to be associated with favorable outcomes, and it is currently evaluated, in combination with interferon β, in patients with MERS-CoV infection [**11-13**]. Cao B 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 percentages of patients with detectable viral RNA, were detected. 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 [**14**]. Furthermore, an open-label, randomized clinical trial, which will compare the efficacy of lopinavir/ritonavir vs. hydroxychloroquine in 150 patients with mild COVID-19, is currently ongoing in the Republic of Korea [**15**]. 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 [14,**16**].

Remdesivir has been recently recognized as a promising antiviral drug against a broad-spectrum of RNA viruses (including MERS-CoV) infection in cultured cells [**17**], mice and non-human primate models [**18**]. 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, not demonstrating a clinical efficacy. Antiviral activities were also demonstrated against single-stranded RNA viruses, including MERS and SARS-Cov [**19**]. Recent results of a preclinical study indicated that, in vitro, the association remdesivir/chloroquine could be highly effective in controlling the SARS-Cov-2 infection [**20**]. The efficacy and safety of the remdesivir are currently evaluated in a phase 3 clinical trial in 453 patients with COVID-19 which will end in May 2020 [**21**]. In addition, a further phase 3 trial is evaluating the efficacy and safety of remdesivir in 1,000 patients with COVID-19; this study will end in May 2020 too [**22**]. 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, resulting in their full recovery [**23**]. Currently the drug is administered among 12 Italian clinical centers [**24**]. Lastly, a case report highlighted promising results of this treatment in the first US patient with COVID-19 [**25**].

Favipiravir is a further 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 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 [**26**]. 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 [**27**]. As reported by Watanabe et al. [**28**], 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 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 of other patients. Chang Chen et al. [**29**] recently published the results of a randomized clinical trial (Chictr.org.cn, n. ChiCTR200030254), which compared the efficacy and safety of favipiravir vs. umifenovir in the treatment of 240 patients with COVID-19, hospitalized in 3 hospitals from 20 February 2020 to 12 March 2020. The 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 to 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, multi-center randomized controlled trial in combination with tocilizumab [**30**]. 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 program to assess the efficacy and safety of favipiravir is appropriate [**31**].

Further antiviral agents are considered as potential treatments in 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 [**32**]. Based on the results of preclinical studies demonstrating inhibitory effects mediated by this combination on SARS-CoV-2 [**33,34**], this drug is currently evaluated in some clinical studies [**35,36**]. Lastly, an analysis carried out by Jeffrey K Aronson of clinical trials on COVID-19 revealed that there are currently more than 20 studies investigating the efficacy of further 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) [**37**]. Sofosbuvir, galidesivir and tenofovir showed promising results for use against the newly emerged strain of coronavirus [**38**]. 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 [**8**]. Even though few evidence have reported 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 patients with severe COVID-19 [**39**].

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 postoperative 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 an ACE2 receptor in the cell membrane. S protein is divided into S1 and S2 by a protease derived from human cells. S1 binds to its receptor, 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 drugs are able to inhibit the enzymatic activity of TMPRSS2 [**5,40**]. A randomized, placebo-controlled clinical trial (CamoCO-19) is evaluating the efficacy and safety of camostat mesilate in 180 patients with COVID-19 [**41**]. Furthermore, both drugs will be evaluated in clinical trials launched by the University of Tokyo [**42**]. Camostat seems well tolerated; common adverse events include rashes, gastrointestinal disorders and changes in liver enzymes. Rare adverse events are thrombocytopenia, liver failure and hyperkalemia. Camostat mesilate was associated to a case of acute eosinophilic pneumonia [**43**]. Another glycoprotein involved in the passage of the virus inside the cell is CD147, which interacts with S protein. CD147 also shows pro-inflammatory activity and takes part in the regulation of cytokine secretion and in leukocytic chemotaxis during viral infections [**44**]. 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 [**45**].

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 hours and by 99.8% after 48 hours. Currently, tests were carried out only *in vitro*and clinical trials are strongly need 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 [**46**].

2. Immunomodulatory and anti-inflammatory agents

As previously reported the SARS-Cov-2 infection can be associated, especially in severe form, to 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 interleukin-6 receptor (IL-6R), of the metabolism, motility and chemotaxis of polymorphonuclear cells, of Janus kinase (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 [**47**]. 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 [**48,49**]. The drug was first tested in China to reduce lung complications in

21 patients with severe SARS-CoV-2 infection [**50**]. The treatment was associated with a reduction of oxygen requirement, resolution of computed tomography (CT) lesions, normalization of lymphocyte count, reduction of C-reactive protein levels, 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 [**51-53**]. Sarilumab belongs to the same drug class of tocilizumab and 3 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 [**54-56**].

Two other drugs, chloroquine and hydroxychloroquine, are commonly off-label used in Chinese and Italian clinical centers for the treatment of COVID-19 [**57**]. 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 [**58**]. Some preclinical studies showed that chloroquine has antiviral activity against SARS coronavirus [**59**], human coronavirus OC43 [**60**] and influenza A H5N1 [**61**] suggesting a possible role in SARS-Cov-2 infection [**62,63**]. Further studies found that chloroquine interferes with terminal glycosylation of the functional ACE 2 receptor, 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 [**20,64,65**]. 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 the patient, particularly in cases of cardiac conduction disorders, glucose-6-phosphate dehydrogenase deficiency or the presence of other concomitant therapies [**66**].

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 [**67-71**]. On March 2020 a phase 3 clinical study (COLCORONA) began. This study will enroll 6,000 outpatients with COVID-19 with the following characteristics: age [?] 40 years; diagnosis of COVID-19 in the past 24 hours; 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 hours, dyspnea, pancytopenia or high neutrophil count and low lymphocyte count; patients not of childbearing age or using contraception methods [**72**].

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 hematopoiesis, 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 [**70**]. A study published in The Lancet suggested that this drug could represent an additional therapeutic alternative for the treatment of COVID-19 [**73**]. A non-randomized phase II clinical trial 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 [**74**]. 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 interferon-γ and IL-6, and virus endocytosis [**75-78**].

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 edema [**79-81**]. In a clinical study, 8 patients with severe ARDS

were treated with ascending doses of the VIP. Of these patients, 7 were successfully extubated and were alive at the five-day time point, 6 left the hospital and 1 died due to a cardiac event [**82**]. 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 hemolytic uremic 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 the inhibition of complement activation might potentially work as a therapeutic approach [**83-85**]. 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 [**86**]. A phase 2/3 randomized, open-label, study is investigating the efficacy and safety of emapalumab, a monoclonal antibody targeting interferon gamma (IFNγ), and anakinra, an antagonist of IL-1R, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection [**87**]. This study received the approval by the AIFA [**88**].

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 is reported that, according to the results of a systematic review of observational studies, the use of corticosteroids in patients with SARS was not associated to survival benefit [**89**]. Similarly, a further systematic review of observational studies found a higher risk of mortality and secondary infections with corticosteroids administered in patients with flu [**90**]. However, this effect was not confirmed by a subsequent study [**91**]. 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 [**92**]. Literature data support that corticosteroids do not add clinical benefits in the treatment of COVID-19 infection [**93**]. 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 [**94,95**], while one case reports described positive effects of methylprednisolone on clinical outcomes of one patient with COVID-19 [**96**]. In conclusion, considering that evidence available is quite conflicting regarding to the use of corticosteroids in patients with COVID-19, as recommended by the WHO, their use should underwent a case by case evaluation.

3. 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 [**97,98**]. The study was launched on February 2020 to verify its efficacy in combination with thymosin in 120 patients with severe pneumonia associated with lymphocytopenia [**99**].

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 [**100,101**]. A key role of VEGF in acute lung injury and ARDS was confirmed [**102**]. 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) [**103,104**].

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 [**105,106**] by modulating TNF-a-induced replication. Moreover, thalidomide suppresses the production of proinflammatory cytokines such as TNF-alpha and IL-

8 through the inhibition of NF-$\varkappa$B [**107**]. Two studies are currently testing its efficacy in patients with COVID19 [**108,109**].

In addition, other drugs are currently evaluated in Chinese clinical trials involving patients with COVID-19, including fingolimod [**110**], high-dose Vitamin C, adalimumab, piperaquine, and leflunomide [**111**]. 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 [**112**].

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 [**113**] and intravenous immunoglobulin purified from IgG antibodies of patients who recovered from COVID-19 [**114**]. Finally, the development of a vaccine against SARS-CoV-2 is urgently needed. However, according to Shang W et al., researchers would bring a new SARS-CoV-2-based vaccine in approximately 16–20 weeks [**115**]. On March 2020, there were 2 candidate vaccines in phase 1 development (studies ChiCTR2000030906 and NCT04283461) and 42 candidate vaccines in preclinical phase of evaluation [**116**]. 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 [**117**]. Furthermore, an experimental mRNA vaccine against the pandemic coronavirus was already administered to one person in US [**118**].

4. 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, chloroquine and tocilizumab, clinical evidence from literature and real life settings support their favorable efficacy and safety profile in improving patients' clinical conditions.

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 this drug 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 [**119**].

Worldwide regulatory agencies are promoting all interventions to ensure strategic coordination and 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$^{\text{th}}$ the EMA and the US FDA jointly chaired the first global regulatory meeting experts to support proceeding to first-in-human clinical studies [**120**]. Since SARS-Cov-2 is still an unknown virus, we are now learning its transmission mechanisms, clinical spectrum of disease, diagnostics and lethality. While waiting for the results of clinical studies demonstrating the efficacy of drugs able to reduce symptoms and complications of COVID-19, the best therapeutic path to pursue is the development of an effective vaccine able to prevent this infection.

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Competing Interests' Statement:

None

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