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Potential COVID-19 Therapeutics: A Perspective on Pharmacological Properties and Safety

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Abstract

There are no guidelines for pharmacological treatment of COVID-19 disease, but several drugs are being tested every day in search of an optimal therapeutic strategy.

The drugs that have been tested, so far, include some antiviral drugs such as danoprevir, favipiravir, darunavir, nelfinavir, remdesivir, umifenovir and the combination lopinavir/ritonavir. Others are drugs targeting inflammatory mediators such as meplazumab, siltuximab, tocilizumab, azithromycin and corticosteroids. Also included in this array of tested drugs are those with pleiotropic actions against SARS-CoV-2 infection like chloroquine/hydroxychloroquine, ivermectin and nitazoxanide, postulated as inhibitors of several phases of virus life cycle.

Upon diagnosis of SARS-CoV-2 infection, it is pertinent to embark on a treatment approach based on potential antiviral options, adequately managed under proper medical situation. We suggest that, in addition to the antiviral option efforts, drugs targeting inflammatory mediators should be considered.

Keywords: Adverse Reaction, COVID-19, Pharmacology, Therapeutics.

Viral Infections

Communicable diseases have been present since the beginning of humanity. In the last decades, the world has grappled with several different epidemics and pandemics. Among these epidemics and pandemics, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), both belonging to coronavirus group, can be highlighted. Others worthy of mention are HIV virus, first described in 1981 and recognized as an epidemic in Africa in 1983 [1], and Zika, transmitted by *Aedes aegypti* mosquito, that heralded its first outbreak in 2007 in Micronesia [2]. In the recent realm of imaging infections with epidemic and/or pandemic status were the non-circulating pathogen, A-H1N1 influenza virus, of animal origin which combines viral genes of swine, avian and human flu, that made its debut in 2009 and which is similar to the virus that in 1918-1919 caused the Spanish flu [3], and Ebola, transmitted by close contact with infected animals such as chimpanzees, gorillas, fruit bats, monkeys, antelopes, and porcupines. The 2014-2016 of Ebola outbreak began in Africa and later reported in different countries [4].

Most of the emerging viral diseases have as their origin or reservoir, some animal species, all with their own transmission mechanisms, particular ways of inducing pathologies and different biology. All are capable of initiating rapid spread in humans and can sprout into epidemics or pandemics. These diversities demand specific responses based on scientific knowledge and adapted for each viral agent.

COVID-19

COVID-19, the current pandemic that is presently barraging afflictions to millions of people is caused by a type of coronavirus, which belongs to the Coronaviridae family, with a positive-sense single-stranded RNA genome. The coronaviridae family infects a wide variety of host species and is classified into four genres, α, β, γ and δ depending on the genomic structure. α and β coronaviruses infect only mammals and, in lesser degree, are responsible for the common cold and croup in children. In contrast, the Middle East respiratory syndrome coronavirus (MERS-CoV) and the severe acute respiratory syndrome (SARS-CoV) are β coronavirus class [5]. Due to its characteristics, the origin is traced to bat-infected coronaviruses acquired from an unknown mammalian host intermediate, from which it was passed on to humans.

COVID-19 outbreak began early December, 2019 in Wuhan, Hubei Province, China as a case of pneumonia of unknown etiology suffered by a patient. On January 7, 2020, the pathogen was identified as a new coronavirus nicknamed SARS-CoV-2 and by etymological nomenclature, the disease was called COVID-19. In January 30 of the same year, the World Health Organization (WHO) declared it a public health emergency of international interest [6]. By the end of May 2020, the official data from the WHO reported 6,160,299 confirmed cases and 371,006 deaths. Based on this report, America remained the most affected region with more than 2.4 million confirmed cases, followed by Europe with 2,061,828. On country basis, the highest number of cases were registered in the United States of America, Russian Federation, Brazil, the United Kingdom and Spain, with an overall mortality of 6.4%. Countries with appreciably high number of registered deaths were the United States of America, the United Kingdom, Italy, France, Spain, Brazil, Belgium, Germany, Iran and Mexico [7].

Clinical Symptoms

In COVID-19, respiratory manifestations are conditions that occur most frequently, however there is a large percentage of patients with different symptomatic debuts and many with asymptomatic status. A prospective observational study in New York with 257 patients with a laboratory diagnosis of SARS-CoV-2 infection reported shortness of breath (dyspnea), fever, cough, myalgia, diarrhea, runny nose, sore throat and headache [8], thus highlighting the typical clinical symptoms of COVID-19. Nonetheless, it should be clarified that in older adults and people with medical comorbidities, the presentation of fever and other respiratory symptoms may be delayed [9]. Initially, acute loss of smell (anosmia) and taste (ageusia) were not considered important symptoms of the disease. In Korea, a telephonic survey of 3,191 patients focused on symptom data recollection showed that acute anosmia or ageusia was observed

in 15.3% of the patients at the initial stage of the disease and in 15.7% of severely ill patients. Another multicenter study, performed in Europe on patients with confirmed diagnosis of SARS-CoV-2 infection reported that, in addition to the typical dyspnea, chest pain, fever, cough and myalgia, more than 80% of them showed manifestations of olfactory and gustatory dysfunctions [10]. Hence, these two symptoms, anosmia and ageusia, should undoubtedly be part of the clinical picture in the diagnosis of COVID-19, particularly at the beginning of the disease [11].

Diagnosis

The clinical symptoms of COVID-19, previously outlined, remain the key clue to suspect SARS-CoV-2 infection, but the confirmatory diagnosis hinges on auxiliary diagnostic tools of imaging studies such as radiological images. Patients with COVID-19 may show radiological changes at the onset of the symptoms. Chest radiograph of the patients has revealed opacities with a bilateral reticular pattern on a ground-glass-like background [12]. This finding is buttressed by a Wuhan retrospective study where bilateral pneumonia, multiple mottling and ground-glass opacity were reported, in addition to pneumothorax seen in one patient. The same pattern of opacities on a bilateral ground-glass-like background with peripheral distribution, multilobar involvement and delimitation was observed in greater detail in chest Computed Tomography (CT), even in patients who have just started with symptoms, characteristics that are not appreciated in chest radiography [13]. Nonetheless, the chest CT imaging pattern is non-specific for COVID-19, since it overlaps with other infections, therefore, its employment in the diagnosis of COVID-19 may lead to misdiagnosis. Based on this variability in chest imaging findings, we propose that chest radiography or CT alone is not absolutely reliable to make the diagnosis of COVID-19. This proposal is in line with the American College of Radiology that refuted the recommendation of CT for the detection or as a first-line test for the diagnosis of COVID-19.

In an effort to find a reliable and an effective diagnostic tool for SARS-CoV-2, the Centers for Disease Control and Prevention (CDC) employed the transcriptase invers polymerase chain reaction test (RT-PCR), which determines the number of replications of cycle threshold cycles (Ct) needed to produce a signal flourishing, with lower Ct values representing higher viral RNA loads. This method is performed by samples with nasopharyngeal swabs, or other samples from the upper respiratory tract [14]. The CDC diagnostic approach was approved and authorized by the Food and Drug Administration (FDA) department of United States. Hence, the standard diagnosis of SARS-CoV-2 is a laboratory test.

Pharmacological Options

Many pharmacological treatment options for SARS-CoV-2 have been postulated and are speculatively being tried in hospitals all over the world. Therefore, no specific drug has been developed for the treatment of patients with SARS-CoV-2. Definitely, this situation has been posing a great challenge both for the science and for the world in general making them to channel lots of endeavors to finding and providing specific therapy against COVID-19. In this effort, works on clinical investigations to evaluate the efficacy of the different proposed drugs and to look for evidence for their approval to be used in patients infected with SARS-CoV-2. Currently, all the pharmacological treatments that have been proposed are based on the experiences accumulated in the management of infectious diseases similar to SARS-CoV-2.

The therapeutic approaches so far employed emanate from the knowledge on the behavior and replication of the virus within the cell. Virus replication is a cycle with key processes. 1. Fixation, which is the ability to bind to the host's receptors, 2. Penetration, which refers to the ability of the virus to introduce into the host`s cell (endocytosis), 3. Biosynthesis, which entails nuclear replication and maturation inside the host cells, and 4. Rapture of the host cell and release of viral replicates. Coronavirus has 4 structural proteins on its surface. These structural proteins are the Spike (S), the Envelope (E), the Membrane (M) and the Nucleocapsid (N) [5]. The S protein structure is made up of two subunits S1 and S2. S1 is the receptor-binding unit (the angiotensin-converting enzyme 2 (ACE2)), and S2 is the viral-host cell fusion unit. This process is activated by transmembrane serine protease 2 (TMPRSS2) to encode the replicase-transcriptase complex that allows the virus to synthesize dependent RNA. Any effective treatment must target to one or more of these replication steps (Figure 1, modified from Sanders et al. [15])

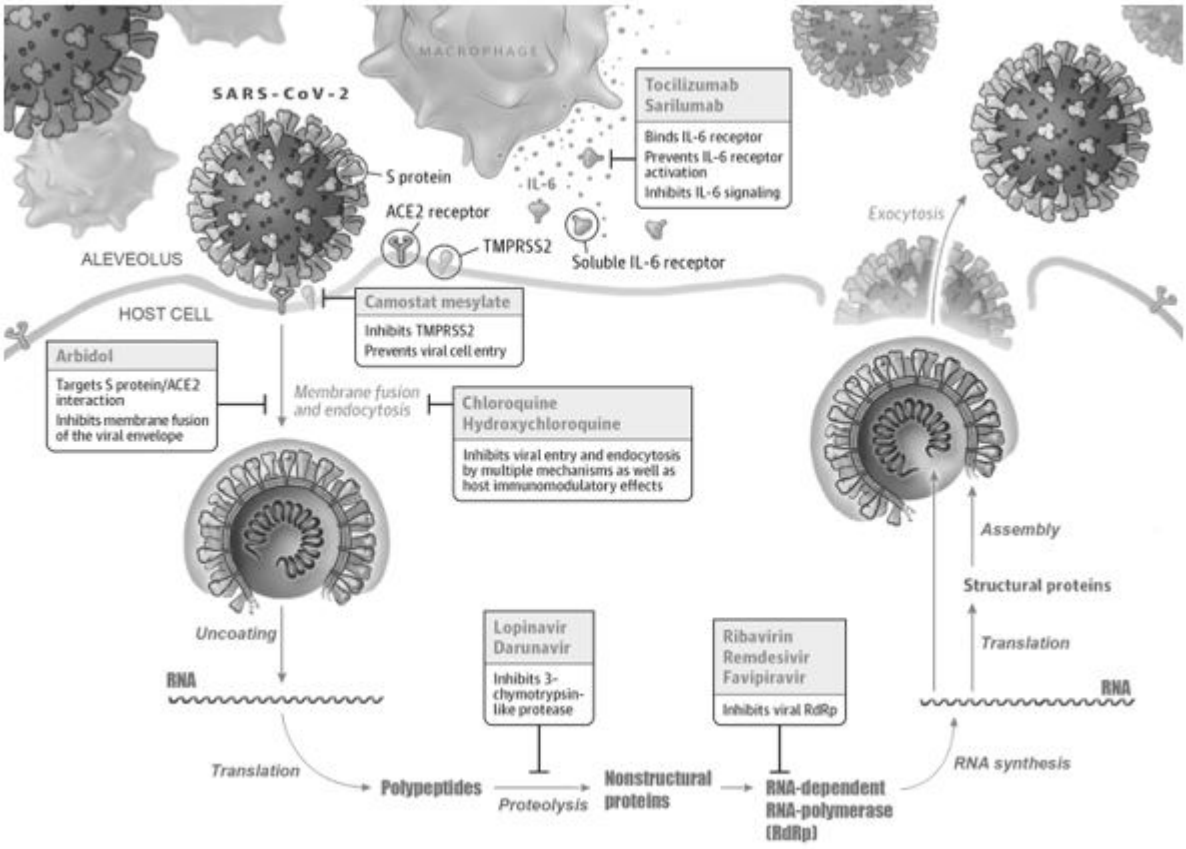

Figure 1: Pharmacological actions for coronavirus disease 2019 (COVID-19)

Antiviral Drugs

Danoprevir

Mechanism of action: Danoprevir [16] belongs to the protease inhibitors antiviral family. Pharmacokinetics: Oral administration. It is a substrate of cytochrome P450 (CYP) 3A. The co-administration of inductors or inhibitors of CYP3A modifies its plasmatic concentrations.

Pharmacodynamics: Danoprenavir has antiviral activity against hepatitis C virus (HCV).

Safety profile: The most frequent adverse effects are anemia, fever, fatigue, headache, influenza-like symptoms, dizziness, rash, diarrhea and decrease in appetite.

Approved indications: Hepatitis C virus.

Evidence against SARS-CoV-2: There is no evidence to support a recommendation on its therapeutic use, its effectiveness is being evaluated in various randomized clinical trials.

Favipiravir

Mechanism of action: Favipiravir [17] belongs to the RNA polymerase inhibitors antiviral family.

Pharmacokinetics: Oral administration. The parent drug undergoes hepatic metabolism mainly by aldehyde oxidase and partially by xanthine oxidase producing an inactive metabolite excreted by the kidneys. It increases the area under the curve of acetaminophen. Certain drugs possess a high inhibitory activity against aldehyde oxidase and could modify favipiravir plasmatic concentrations. Example of such drugs are loratadine, ondansetron, verapamil, ketoconazole and amlodipine [18].

Pharmacodynamics: Favipiravir inhibits the replication of viral genome. The antiviral activity is efficacious against a wide range of RNA viruses such as influenza, Machupo, sandfly fever, yellow fever, polio, rhino and respiratory syncytial virus.

Safety profile: Mild to moderate diarrhea, asymptomatic increase of blood uric acid and transaminases, decrease in the neutrophil counts.

Approved indications: Influenza.

Evidence against SARS-CoV-2: Clinical trial conducted in Shenzhen with eight patients showed shorter viral clearance and a higher rate of improvement in chest imaging [18].

Darunavir

Mechanism of action: Darunavir [19] belongs to the protease inhibitors antiviral family.

Pharmacokinetics: Oral administration. The drug metabolism is mediated by cytochrome P450 (CYP) 3A4. The co-administration of inductors or inhibitors of CYP3A modifies its plasmatic concentrations. Darunavir excretion is mainly by feces and in a lesser degree through the urine.

Pharmacodynamics: Darunavir inhibits the dimerization of viral protease and its catalytic activity.

Safety profile: Diarrhea, rash, nausea, headache.

Approved indications: HIV- infected subjects.

Evidence against SARS-CoV-2: There is no quality evidence to support a recommendation on its therapeutic use. The effectiveness is being evaluated in various randomized clinical trials.

Nelfinavir

Mechanism of action: Nelfinavir [20] belongs to the protease inhibitors antiviral family.

Pharmacokinetics: Only oral administration. The concentrations are higher if the drug is taken with food. Its metabolism is mainly mediated by cytochrome P450 (CYP) 3A, and in a lesser degree by CYP2C19, 2D6 and 2C9. The plasma half-life of nelfinavir is approximately 4 hours. The drug excretion is mainly by feces and in urine in lesser degree.

Pharmacodynamics: Darunavir inhibits the dimerization of viral protease and its catalytic activity.

Safety profile: The most common adverse reaction is diarrhea. As other protease inhibitors, several metabolic problems such as hyperlipidemia, hyperglycemia and the development of diabetes have been noted.

Approved indications: HIV- infected subjects.

Evidence against SARS-CoV-2: There is no quality evidence to support a recommendation on its therapeutic use. The effectiveness is being evaluated in various randomized clinical trials.

Remdesivir

Mechanism of action: Pro-drug belonging to the nucleotide analogue family. It inhibits viral RNA-polymerase.

Pharmacokinetics: Its administration is intravenous. The formulation includes cyclodextrin, a vehicle that can deteriorate the renal function [21].

Pharmacodynamics: Remdesivir has demonstrated *in vitro* activity against SARS-CoV-2 and against other coronaviruses such as SARS and MERS-CoV [22].

Safety profile: The described adverse reactions include increased hepatic enzymes, diarrhea, rash, renal failure and hypotension. Approved indications: None.

Evidence against SARS-CoV-2: There is no quality evidence to support a recommendation on its therapeutic use. The effectiveness is being evaluated in various randomized clinical trials. A recent study in 53 patients with severe COVID-19 showed 68% of ventilatory improvement [23].

Umifenovir (Arbidol)

Mechanism of action: Umifenovir [24] inhibit viral glycoprotein conformational changes during membrane fusion by interacting with the phospholipid membrane and aromatic residue-enriched protein motifs.

Pharmacokinetics: The administration is oral. The drug and its active metabolites have long plasmatic half-life, 25 hours. Multiple enzymes, including CYP1A2, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5, FMO1, FMO3 and FMO5 were capable of metabolizing it.

Pharmacodynamics: Umifenovir is a broad-spectrum antiviral drug that is used clinically to treat influenza.

Safety profile: The principal adverse effects observed were mild gastrointestinal disturbances like diarrhea and nausea [24].

Approved indications: Prophylaxis and treatment of influenza virus A and B infection. Recent studies have extended the inhibitory activity of arbidol to other human viruses such as hepatitis B and C viruses, rhinovirus, chikungunya virus, and respiratory syncytial virus.

Evidence against SARS-CoV-2: There is no quality evidence to support a recommendation on its therapeutic use. The effectiveness is being evaluated in various randomized clinical trials.

Lopinavir/ritonavir

Mechanism of action: Pharmacological combination of protease inhibitors.

Pharmacokinetics: The drugs exhibit intense hepatic metabolism. Ritonavir inhibits CYP3A4 activity and increases lopinavir plasmatic concentrations. The elimination of the drugs is mainly in feces.

Pharmacodynamics: Lopinavir/ritonavir combination exhibits antiviral effect in HIV infection. Preclinical studies have demonstrated activity against SARS and MERS [25].

Safety profile: Side effects include gastrointestinal alterations as diarrhea, nausea and vomit. Clinical findings suggest an increased risk of pancreatitis and hepatotoxicity due to lipids impairment.

Approved indications: HIV infection.

Evidence against SARS-CoV-2: A randomized trial in 199 patients have shown no difference in time to clinical improvement or mortality in severe COVID-19 patients [26].

Drugs Targeting Inflammatory Mediators

Siltuximab

Mechanism of action: Siltuximab is an anti-IL-6 chimeric human-mouse monoclonal antibody.

Pharmacokinetics: It is administered intravenously and reaches 0.06 L/kg volume of distribution. Total body clearance is 0.23 L/day without interference by hepatic nor renal impairment [27].

Pharmacodynamics: This monoclonal antibody binds to serum IL-6 in order to block its binding to Il-6 soluble and membrane receptors. IL-6 is found to be an upregulated mediator in multiple autoimmune diseases and neoplasms [28].

Safety profile: Common side effects that have been described includes hypertriglyceridemia, hypercholesterolemia, hyponatremia, hypophosphatemia, hypocalcemia, herpes zoster, diarrhea, pruritus, neutropenia, lymphopenia, polycythemia and fatigue [28]. Other findings were mild serum aminotransferase elevations, upper airway viral infections, maculopapular rashes and neuropathy [29]. The long-term treatment (~ 90 months) is well tolerated in most of the patients.

Approved indications: It is indicated to treat multicentric Castleman disease in patients without HIV or herpesvirus-8 infection.

Evidence against SARS-CoV-2: There is a few evidences related to the use of siltuximab against SARS-CoV-2 infection. However, it is proposed that blocking IL-6 will ameliorate the cytokine storm, lung injury and consequent multiple organ failure. An Italian study reported improvement of patients using siltuximab as a compassionate treatment and that almost 76% of the recruited patients improved or stabilized their condition [30]. There are various studies evaluating siltuximab alone and in combination with other drugs like methylprednisolone, anakinra and tocilizumab [31].

Tocilizumab

Mechanism of action: Tocilizumab is an anti-IL-6 receptor humanized monoclonal antibody.

Pharmacokinetics: It is administered subcutaneously or by intravenous infusion. Tocilizumab can inhibit CYP1A2, CYP2C9, CYP2C19 and CYP3A4, thus, care must be taken in the prescription of drugs metabolized by these cytochromes when taking tocilizumab. Its elimination is dose dependent with long half-life ranging from 1 to 2 months [32].

Pharmacodynamics: Tocilizumab binds to IL-6 receptor, both soluble and membrane-bound, inhibiting the activity of the cytokine, thus reducing the associated pro-inflammatory cascade [32].

Safety profile: Tocilizumab monotherapy is well tolerated. The common adverse reactions include upper respiratory tract and skin infections, hypercholesterolemia, neutropenia and injection-site reactions. There are special concerns about tocilizumab and the incidence of gastrointestinal perforations, elevation of transaminase levels and cardiovascular events [32].

Approved indications: Rheumatoid arthritis, systemic juvenile idiopathic arthritis and polyarticular juvenile idiopathic arthritis.

Evidence against SARS-CoV-2: Just one study has been published since the SARS-CoV-2 outbreak demonstrating that tocilizumab treatment can improve clinical status by lowering oxygen intake, improving lung CT scans, correcting lymphopenia and decreasing C-reactive protein. Obvious limitation of this study were a limited number of patients and other bias related to the treatment administered to the patients [33].

Azithromycin

Mechanism of action: Antibiotic member of the macrolide family. Azithromycin inhibits bacterial protein synthesis [34].

Pharmacokinetics: Oral administration. It is absorbed rapidly. Food reduces its plasma concentrations. It is extensively distributed in all tissues except the brain and cerebrospinal fluid leading to high concentrations within cells, especially tissue fibroblasts that act as a reservoir, resulting in much greater concentrations. Azithromycin undergoes hepatic elimination and only 12% of the drug is excreted unchanged in the urine. The elimination half-life reaches 40–68 h because of its accumulation in tissues [35].

Pharmacodynamics: The bacteriostatic antimicrobial activity of azithromycin results from the inhibition of protein synthesis by reversibly binding at the exit site E of in the 50S subunit of the bacterial ribosome [36]. Azithromycin exerts immunomodulatory effects by decreasing the production of proinflammatory cytokines such as IL-8, GM-CSF, IL-6, MMP, IL-1β and TNF-α [38]. Also, diminished adhesion molecule expression as well as increased mucociliary clearance and reduced goblet cell secretion have been described [37].

Safety profile: In general, its well tolerated but in some patients can cause abdominal pain, diarrhea, flatulence, nausea, vomiting, increased liver enzymes, headache and abnormal vision. In our actual paradigm, azithromycin is used with chloroquine, a combination which is associated with cardiac alterations such greater changes in QTc interval [38].

Approved indications: FDA approved uses includes bacterial infections such as acute infective exacerbation of chronic obstructive pulmonary disease, acute otitis media, bacterial conjunctivitis, chancroid, *Chlamydia trachomatis* infection, community acquired pneumonia, gonorrhea, infection of skin and/or subcutaneous tissue, streptococcal pharyngitis and tonsillitis [38].

Evidence against SARS-CoV-2: In patients with non-cardiogenic acute or moderate acute respiratory distress syndrome, use of azithromycin was reported to be associated with decreased 90-day mortality and faster ventilator discontinuation [39]. Arabi *et al.* [40] in a cohort study reported that the use of azithromycin was not significantly associated with a reduction in 90-day mortality or improvement in Middle East Respiratory Syndrome coronavirus RNA clearance. There are many trials registered and recruiting trying to evaluate the efficacy and safety of azithromycin in SARS-CoV-2 infection. Many of the studies administers Azithromycin and hydroxychloroquine, while others combine it with oseltamivir or vitamins.

Drugs Showing Pleiotropic Actions Against SARS-COV-2 Infection

Chloroquine/hydroxychloroquine

Mechanism of action: Chloroquine (CQN) and the structural analogs such as hydroxychloroquine (HCQN) have been widely described as showing potent immunomodulation effects, and reduces IL-1, IL,6, TNF and IFN [41]. Also, the antiviral properties against RNA viruses such as Poliovirus, Influenza, Dengue and Ebola have been described. The purported mechanism of action includes interference at the union of the virus to the cellular surface, endocytosis prevention and fusion suppression with the endosome.

Pharmacokinetics: CQN and HQN have oral administration and are extensively absorbed. The elimination half-life is very long (40-50 days). The elimination is mainly renal and only small amounts are eliminated by bile, sweat and saliva [42].

Pharmacodynamics: An antimalarial, but in addition is now broadly used in autoimmune diseases such as lupus and rheumatoid arthritis.

Safety profile: The adverse reactions include gastrointestinal alterations, retinopathy, skin hyperpigmentation, myopathy, cardiomyopathy and cardiac arrhythmias (QT prolongation) [43].

Approved indications: Malaria, rheumatoid arthritis, lupus.

Evidence against SARS-CoV-2: Chloroquine is highly effective in the control of 2019-nCoV infection in vitro. At least 16 different trials for SARS-CoV-2 propose the use chloroquine or hydroxychloroquine in the treatment of COVID-19. In a recent publication result from more than 100 patients, it was demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course [44].

Ivermectin

Mechanism of action: Antiparasitic drug with a potent activity against a broad spectrum of nematodes, helminths and some arthropods.

Pharmacokinetics: Ivermectin absorption is incomplete when administered orally. However, its high lipid solubility increases its bioavailability by 2.5-fold when administered with high fat meal [45]. The chemical characteristics makes it to be widely distributed in the tissues. It is metabolized in liver by CYP3A4 and excreted mainly in feces. Its half-life ranges from 12 to 54.5 h., but a population pharmacokinetics model has estimated its $t_{1/2}$ into a mean of 38.9 h [46].

Pharmacodynamics: In parasites, it increases the chloride conductance in cells resulting in hyperpolarization which diminishes action potentials and blocks the vital functions such as locomotion [45].

Safety profile: Patients taking ivermectin experience almost no serious adverse effects. Most of the side effects include headache, dizziness, muscle pain, nausea and diarrhea. Because of its activity of gamma-aminobutyric acid receptor agonism, ivermectin can produce effects like encephalopathy, confusion, stupor and coma [45].

Approved indications: *Onchocerca volvulus* infection, intestinal strongyloidiasis, pediculosis capitis and rosacea with inflammatory lesions.

Evidence against SARS-CoV-2: It has demonstrated *in vitro* antiviral activity against some viruses like influenza virus, dengue virus, Venezuelan equine encephalitis virus, West Nile virus and HIV-1. Recently, ivermectin showed *in vitro* antiviral activity against SARS-CoV-2. It has been suggested that this effect is associated with the inhibition of importin α/β1 heterodimer that transport viral proteins into the nucleus [47].

Nitazoxanide

Mechanism of action: Nitazoxanide inhibits pyruvate-ferredoxin oxidoreductase enzyme-dependent electron transfer reactions, thus disrupting anaerobic metabolism in pathogens [48].

Pharmacokinetics: It is well absorbed orally and is rapidly hydrolyzed into tizoxanide, which is the active metabolite. Tizoxanide conjugates with glucuronide in liver and is eliminated by urine and bile. It binds widely to serum proteins. The half-life is approximately 1.3 h [48].

Pharmacodynamics: Nitazoxanide has demonstrated *in vitro* antiviral activity against MERS and SARS-CoV-2 [49].

Safety profile: Nitazoxanide is a safe and tolerable drug in regular doses. Regarding its pharmacokinetics, nitazoxanide or its metabolite tizoxanide does not inhibit microsomal enzymes. The most frequent adverse effects are those related to disorders of the gastrointestinal system, which include abdominal pain, diarrhea and nausea [50]. Long-term use of nitazoxanide has not been evaluated extensively, however, a study reported that patients have ingested 500 mg twice daily for 24 weeks without significant adverse reactions [50].

Approved indications: Antiprotozoal agent against *Cryptosporidium parvum* and *Giardia intestinalis* infection [48].

Evidence against SARS-CoV-2: In preclinical studies, tizoxanide inhibits replication of diverse respiratory viruses like parainfluenza virus, syncytial respiratory virus, coronavirus, rotavirus, norovirus, human immunodeficiency virus, Ebola virus, dengue virus, yellow fever virus, Japanese encephalitis virus, hepatitis B and C virus [48-49, 51]. Nitazoxanide inhibits proinflammatory cytokine production (TNF-α, IL-2, IL-4, I-5, IL-6, IL-8, and IL-10) in peripheral blood mononuclear cells [49]. Also, it exerts immunomodulatory effects by enhancing the expression of genes involved in the signaling of Toll-like receptors, retinoic acid-inducible gene-like receptors 1, mitochondrial antiviral signaling protein, and genes stimulated by interferon, all of which contribute to the net antiviral effect of the drug by inhibiting the viral replication cycle and improving the innate immunity [48,51]. Some studies propose the use of nitazoxanide for COVID treatment combined with hydroxychloroquine and ivermectin [52], and as a prophylactic agent [53].

Expectations

In this long search and enormous effort to find a drug that really improves health conditions, results of the proposed drugs that buttress their approval or contraindicate their use have been evidenced. Such is the case of hydroxychloroquine and macrolides that more than beneficial effects are associated with cardiotoxic effects [54].

Contrary to the above, Ivermectin, in an *in vitro* study, has shown that antiparasites inhibit host nuclear import and viral proteins, thus, demanding further research on its beneficial effect in humans [55]. In addition to the search for antiviral drugs, adjuvant options such as immunomodulatory therapy are being investigated, which, to date, has not accumulated sufficient evidence to support or contraindicate its use [56]. Experts from national health organizations and institutes argue that the solution to the rapid spread of SARS-CoV-2 virus infections is to provide a specific vaccine against the virus.

Conclusions

Many pharmacological treatment options for SARS-CoV-2 have been postulated and are speculatively being tried in hospitals all over the world. The drugs that have been tested, so far, include some antiviral drugs such as danoprevir, favipiravir, darunavir, nelfinavir, remdesivir, umifenovir and the combination lopinavir/ritonavir. Others are drugs targeting inflammatory mediators such as meplazumab, siltuximab, tocilizumab, azithromycin and corticosteroids. Also included in this array of tested drugs are those with pleiotropic actions against SARS-CoV-2 infection like chloroquine/hydroxychloroquine, ivermectin and nitazoxanide, postulated as inhibitors of several phases of virus life cycle.

Upon diagnosis of SARS-CoV-2 infection, it is pertinent to embark on a treatment approach based on potential antiviral options, adequately managed under proper medical situation. We suggest that, in addition to the antiviral option efforts, drugs targeting inflammatory mediators should be considered.

Abbreviations

ACE2: Angiotensin-converting enzyme 2
COVID: Coronaviridae disease
CT: Computed tomography
CDC: Centers for Disease Control
CQN: Chloroquine
FDA: Food and Drug Administration
HCQN: Hydroxychloroquine
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
H1N1 influenza virus
MERS: Middle east respiratory syndrome
RT-PCR: Real-time polymerase chain reaction
SARS: severe acute respiratory syndrome
SARS-CoV: severe acute respiratory syndrome- coronavirus
WHO: World Health Organization

Declarations

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

Not applicable

Availability Of Data and Material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that there are no competing interests.

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Authors' contributions

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(a) Contributed to the conception of the work. (b) Contributed to the collection, analysis, or interpretation of data. (c) Critically revised the manuscript for important intellectual content. (d) Drafted manuscript. (e) Gave final approval. All authors read and

approved the final manuscript.

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