Journal of Medicine and Biology

Review Article | Vol 3 Iss 2

Clinical Treatment Perspectives for the Management of SARS-CoV-2 Infection

Shipra Singhal[1], Neha Mittal[2] and Vaishali M Patil[1*]

[1]*Computer Aided Drug Design Lab, KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad, India*
[2]*Department of Pharmaceutical Chemistry, Ram-Eesh Institute of Vocational and Technical Education, Greater Noida, India*

Correspondence should be addressed to Vaishali M Patil, vaishali.patil@kiet.edu

Received: September 15, 2020; Accepted: September 28, 2020; Published: October 5, 2020

ABSTRACT

The worldwide pandemic caused by SARS-CoV-2 has created a demand for safe and effective therapeutics to control the spread of viral infection. Various drugs have been investigated using *In-vivo, In-vitro, In-silico* methods and few are in clinical use.

METHODOLOGY

A detailed literature review has been carried out for collecting details on current updates and outcomes from various studies related to clinical use of drugs for the treatment of infection caused by SARS-CoV-2.

RESULTS

Some drugs are being successfully repurposed as anti-COVID therapeutics and are used in clinical practice with moderate to better efficacy. A detailed classification of clinically useful anti-COVID therapeutics based on their mechanism of action is investigated. Some suitable examples are included to discuss the clinical outcomes.

CONCLUSION

The work concludes the role of various COVID-19 targets and their clinical importance. It will provide a detailed guideline for the clinical therapeutics to medical practitioners as well as research scientists.

KEYWORDS

SARS-CoV-2 infection; COVID-19; COVID-19 therapeutics; Clinical drugs; Classification

INTRODUCTION

In late December 2019, few cases of unidentified pneumonia were reported in Wuhan, Hubei Province, People's Republic of China (PRC). The clinical characteristics were found quiet similar to those of viral pneumonia [1]. The pathogen of the outbreak was later identified as a novel beta-coronavirus, named 2019 novel coronavirus (2019-nCoV) and recalled to our mind the

Citation: Shipra Singhal, Clinical Treatment Perspectives for the Management of SARS-CoV-2 Infection. J Med Biol 3(1): 97-113.

terrible memory of the severe acute respiratory syndrome (SARS-2003, caused by another beta-coronavirus) that occurred 17 years ago [2].

In 2003, a coronavirus with the etiology of a mysterious pneumonia, also originated from southeast China, especially Guangdong province was reported. It was named as SARS coronavirus that fulfilled the Koch's postulate [3]. The mortality rate caused by the virus was around 10%–15% [4,5]. Through the years, the medical facilities have been improved; nevertheless, no proper treatment or vaccine is available for the SARS [5]. The emergence of another outbreak in 2012 of novel coronavirus reported in the Middle East and it shared similar pathological features as were observed with the outbreak in 2003 [6]. Both of them were caused by coronaviruses but the intermediate host for MERS is thought to be the dromedary camel and the mortality can be up to 37% [4]. The initial clinical manifestations for both SARS and MERS are usually nonspecific except that the majority of patients presented with fever and respiratory symptoms [1,5]. The newly reported SARS-CoV-2 virus belongs to β-coronavirus, a large class of viruses prevalent in nature. Similar to other viruses, SARS-CoV-2 has many potential natural, intermediate and final hosts. It poses great challenge to prevent its spread and provide treatment to control the viral infection. Compared with SARS and MERS, the SARS-CoV-2 has high transmissibility and infectivity, despite of low mortality rate [7]. Genome analysis of novel coronavirus sequences revealed that the complete genome sequence recognition rates of SARS-CoV and bat SARS coronavirus (SARS-CoV-RaTG13) were 79.5% and 96% respectively [8]. It implies that the coronavirus might originate from bat [9]. With such diverse reports and unavailability of proper therapeutics has created panic all over the world. A limited list of drugs is being used by clinicians to control the infection and other complications associated with it. The vaccines have been successfully placed for clinical trials.

In the present manuscript a detailed view of SARS-CoV-2 virology, clinical symptoms, treatment and preventive strategies including clinically useful therapeutics along with vaccines is discussed.

Virology

Coronavirus is an envelope, positive single-strand RNA virus. It belongs to the *Orthocoronavirinae* subfamily, as the name, with the characteristic "crown-like" spikes on their surfaces [4]. Together with SARS-CoV, bat SARS-like CoV and others also belong to the genus beta-coronavirus. COVID-19 (i.e. 2019-nCoV infection) is classified as a fifth-category notifiable communicable disease in Taiwan on January 15, 2019 [10]. The exact origin, location, and natural reservoir of the 2019-nCoV remain unclear, although it is believed that the virus is zoonotic and bats may be the culprits because of sequence identity to the bat-CoV [4,11]. According to some previous studies on the SARS- and MERS-CoV, epidemiologic investigations, their natural reservoir is bat, while palm civet or raccoon dog may be the intermediate (or susceptible) host for SARS-CoV and the dromedary camel for MERS-CoV [4,11].

The infectious doses for 2019-nCoV is not clear, but a high viral load of up to 10^8 copies/mL in patient's sputum has been reported [12]. The viral load increases initially and can be detected 12 days after onset of symptoms [13]. Therefore, the infectivity of patients with 2019-nCoV may last for about 2 weeks [2].

Epidemiology and pathogenesis

All age groups are susceptible to viral infection. It is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occurs from asymptomatic and/or before the onset of symptoms [12]. The virus can remain viable on surfaces for days in favorable atmospheric conditions but

are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. [14-16]. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by the patient or then touching the nose, mouth and eyes. The virus is also present in the stools and contamination of the water supply and subsequent transmission via aerosolization/feco oral route is also hypothesized [17]. As per current information, transplacental transmission from pregnant women to their fetus has not been described [18]. However, neonatal disease due to postnatal transmission is described [18]. The incubation period varies from 2 to 14 days [median 5 days]. Studies have identified angiotensin receptor 2 (ACE2) as the receptor through which the virus enters the respiratory mucosa, replicates and induces infection [15].

Clinical features

The clinical features of COVID-19 are varied, ranging from asymptomatic to acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. The common clinical features include fever (not in all), cough, sore throat, headache, fatigue, myalgia and breathlessness. Conjunctivitis has also been described. Thus, they are indistinguishable from other respiratory infections. In a subset of patients, by the end of the first week the disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα [1, 8, 19-21]. Fatality rate in hospitalized adult patients ranged from 4 to 11% while World Health Organization (WHO) has estimated 3.4% mortality rate as of August 10, 2020 [22].

Diagnosis

The SARS-CoV-2 virus is usually observed as an acute viral respiratory tract infection and many differential diagnoses related to common viral pneumonia should be considered, such as influenza, parainfluenza, adenovirus infection, respiratory syncytial virus infection, metapneumovirus infection, and atypical pathogens, such as *Mycoplasma pneumoniae* and *Clamydophila pneumonia* infections etc. [1,23].

Therefore, it is crucial to trace the travel and exposure history when approaching a suspected patient back from an epidemic area. In addition, commercial respiratory syndromic diagnostic kits that detect multiple etiological agents may help timely differential diagnosis [2].

Specific diagnosis can be performed by specific molecular tests on the respiratory samples (throat swab/nasopharyngeal swab/sputum/endotracheal aspirates and bronchoalveolar lavage). Virus may also be detected in the stools and in severe cases, the blood[24].

Confirmatory laboratory diagnosis usually rely on a real-time RT-PCR assay to detect viral RNA by targeting a consensus E region of pan beta-CoV or other more specific regions (such as RdRp or N region) [1,8,11]. Chest x-ray and computer tomography (CT) usually revealed bilateral pneumonia (75%-98%) with multiple mottling and ground-grass opacity [1,8]. Routine laboratory data in the early stages of COVID-19 epidemic are similar to common viral infection: lymphopenia, prolonged prothrombin time, elevated D-dimer, liver enzymes (alanine aminotransferase), total bilirubin, and lactate dehydrogenase, with worsening data in critical cases [1]. Leukocytosis may occur if the infection is complicated with secondary bacterial infection. Considering patients' and laboratory safety, physicians should carefully evaluate the necessity of frequent blood sampling and conduct aspiration to prevent the risk of unexpected exposure [2].

Prevention

One of the effective strategy adopted all over the world to control the pandemic spread is adoption and successful implementation of preventive measures such

as social distancing, personal hygiene, and isolation of confirmed or suspected cases with mild illness at home/hospital. The ventilation at home should be good with sunlight to allow for destruction of virus. Patients should be asked to wear a simple surgical mask and practice cough hygiene. Caregivers should be asked to wear a surgical mask when in the same room as patient and use hand hygiene every 15-20 minutes. The greatest risk in COVID-19 is transmission to healthcare workers. In the SARS outbreak of 2002, 21% of those affected were healthcare workers [25]. It is important to protect healthcare workers to ensure continuity of care and to prevent transmission of infection to other patients. While COVID-19 transmits as a droplet pathogen and is placed in Category B of infectious agents (highly pathogenic H5N1 and SARS), by the China National Health Commission and the infection control measures recommended are those for category A agents (cholera, plague). Some of them are -I) placing patients in separate rooms or cohorted together; ii) non-requirement of negative pressure rooms; iii) regular sanitization of the rooms, surfaces and equipments preferably with sodium hypochlorite; and IV) provision of fit tested N95 respirators, protective suits and goggles to healthcare workers. In addition to this the precautions suggested for prevention of airborne transmission should be adopted during aerosol generating procedures such as intubation, suction and tracheostomies. All contacts including healthcare workers should be monitored for development of symptoms of COVID-19. Patients can be discharged from isolation once they are afebrile for at least 3 days and have two consecutive negative molecular tests at the sampling interval of 1 day. These recommendations are different from those suggested for pandemic flu where patients were asked to resume work/school once afebrile for 24 hrs or by day 7 of illness and negative molecular tests were not a prerequisite for discharge.

At the community level, people should be asked to avoid crowded areas and postpone non-essential travel to places with ongoing transmission. They should be asked to practice cough hygiene by coughing in sleeve/ tissue rather than hands and practice hand hygiene frequently every 15-20 min. Patients with respiratory symptoms should be asked to use surgical masks. The use of mask by healthy people in public places has not shown to protect against respiratory viral infections and is currently not recommended by WHO [26]. Some of the guidelines to prevent or slow the transmission of infection includes I) washing hands at regular intervals with soap and water, or clean them with alcohol-based hand rub; ii) maintaining at least 1 meter distance with people coughing or sneezing; iii) avoiding touch to face, iv) covering mouth and nose when coughing or sneezing; v) stay home if you feel unwell or self-isolation; vi) refrain from smoking and other activities that weaken the lungs; and vii) practicing physical distancing by avoiding unnecessary travel and staying away from crowds and gatherings [27].

Clinical useful anti-covid therapeutics

The uncontrolled spread of COVID-19 and increasing number of deaths worldwide is in direct need of effective therapeutics. The urgent requirement for effective therapeutics was supplemented with the use of available drugs and repositioning them as SARS-CoV-2 inhibitors based on clinical outcomes. Among the available or proposed candidate drugs to treat COVID-19, most of them are selected based on the drug repositioning approach of the antiviral therapeutics is an interesting strategy because knowledge on safety profile, side effects, posology and drug interactions is well reported [28,29].

Globally the clinical trials are underway to investigate the efficacy of repurposed drugs in clinical settings. The major drugs are chloroquine/hydroxychloroquine, lopinavir/ritonavir, teicoplanin, brilacidin (PMX-30063), solnatide, remdesivir, meplazumab, leronlimab, darunavir, cobicistat, rintatolimod, plitidepsin,

favipiravir/umifenovir, and IFX-1. Based on the clinical outcomes, side effects and complications observed, some of them have been discontinued from the line of COVID-19 category. The COVID-19 therapeutics and the disease target are summarized in Table 1 and is elaborated in further section of this paper.

Target name	**Therapeutics**
1-Phosphatidylinositol 4,5-bisphosphate phosphodiesterase γ-1 (PLCγ-1)	Lopinavir/Ritonavir
Basigin (CD147)	Meplazumab
Chemokine receptor CCR5	Leronlimab
Complement C5	IFX-1
Defensin (nonspecified subtype)	Brilacidin
Elongation factor 1-α2	Plitidepsin
Envelope protein (SARS-CoV-2; COVID-19)	LV-SMENP-DC
Epithelial sodium channel (ENaC)	Solnatide
Histamine N-methyltransferase	Chloroquine phosphate
Membrane glycoprotein (SARS-CoV-2; COVID-19)	LV-SMENP-DC
Nucleocapsid (SARS-CoV-2; COVID-19 virus)	Lopinavir/ritonavir Darunavir/cobicistat
Protein kinase C α type	Solnatide
RNA-directed RNA polymerase	Remdesivir Favipiravir
Surface glycoprotein (spike glycoprotein) (SARS-CoV-2; COVID-19)	Human COVID-19 coronavirus (SARS-CoV-2) vaccine LV-SMENP-DC
Toll-like receptor 3	Rintatolimod
Tumor necrosis factor ligand superfamily member 6	Lopinavir/ritonavir
Tumor necrosis factor receptor type 6 (FASL receptor; Fas)	ASC-09/ritonavir Lopinavir/ritonavir
Human coronavirus (SARS-CoV-2; COVID-19) proteins	Human COVID-19 coronavirus (SARS-CoV-2) mRNA vaccine

Table 1: Some examples of SARS-CoV-2 targets and name of therapeutics under investigation.

Chloroquine/ Hydroxychloroquine

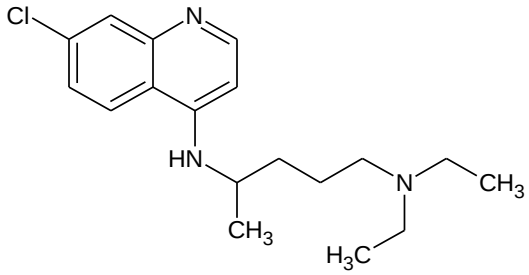

Figure 1: Structure of Chloroquine.

Chloroquine and Hydroxychloroquine have been used for a very long time to treat malaria and autoimmune diseases such as lupus or rheumatoid arthritis. Their adverse effects are well known and can be severe, from psychiatric effects to arrhythmia and sudden death [30].

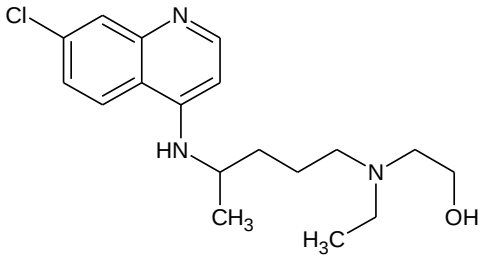

Figure 2: Structure of Hydroxychloroquine

Chloroquine is a cheap and safe drug that has been used for more than 70 years. The anti-viral and anti-inflammatory activities of chloroquine may account for

its potent efficacy in treating patients with COVID-19 pneumonia.In light of the urgent clinical demand, chloroquine phosphate is recommended to treat COVID-19 associated pneumonia in larger populations [31,32].

Several mechanisms have been proposed to assume that chloroquine or hydroxychloroquine may be effective against SARS-CoV-2 [33,34] as detailed below:

1. Cell models of SARS-CoV-1 infection treated with chloroquine show interference with the glycosylation of ACE-2 receptors, proposed as the site of SARSCoV-2 cell binding.
2. Chloroquine/ hydroxychloroquine may increase the pH of acidic cellular organelles, hindering the intermediate stages of endocytosis and virion transport and posttranslational modification of newly synthesized viral proteins.
3. Chloroquine/ hydroxychloroquine can counter the process of virion assembly and viral protein synthesis.
4. One of the study demonstrate that hydroxychloroquine (EC_{50}=0.72 µM) found to be more potent than chloroquine (EC_{50}=5.47 µM) [35]. Some of the studies suggest a synergistic effect with the combination of hydroxychloroquine and azithromycin. Azithromycin has *In-vitro* inhibition against Zika and Ebola viruses [36-38] and to prevent severe respiratory tract infections when administrated to patients suffering viral infection [39]. This finding should be further explored to know whether a combination is more effective especially in severe cases [40]. The dosage regimen and duration of treatment suggests dose up to 20 mg/kg can usually be safe. Typical regimens include administration of 500 mg/day and the typical duration of treatment is around 7 days [41].

Lopinavir/Ritonavir

The antiretroviral protease inhibitor, lopinavir is widely used for the treatment of Human Immunodeficiency Virus (HIV) and is a potential candidate for the treatment of COVID-19. Lopinavir is formulated in combination with another protease inhibitor, ritonavir (lopinavir/ritonavir, branded as kaletra or aluvia). Ritonavir inhibits the metabolizing enzyme cytochrome P450 3A and therefore increases the half-life of lopinavir [42].

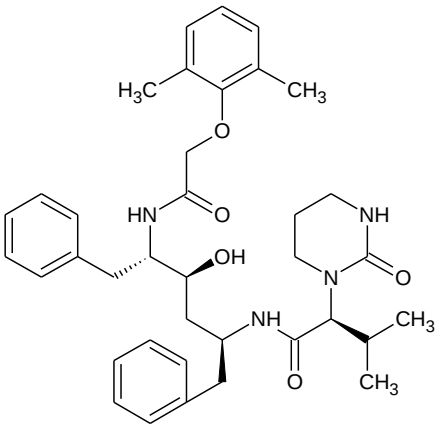

Figure 3: Structure of Lopinavir.

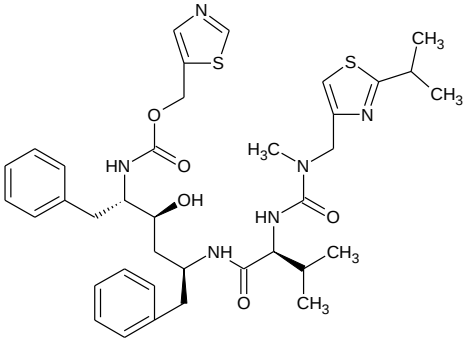

Figure 4: Structure of Ritonavir.

The enzyme 3-chymotrypsin-like protease ($3CL^{pro}$) plays a crucial role in processing the viral RNA [43, 44]. As lopinavir/ritonavir is a protease inhibitor, it may inhibit the action of $3CL^{pro}$, thereby disrupting the process of viral replication and release from host cells [44,45]. Recent evidence suggests that lopinavir has antiviral activity against SARS-CoV-2 as observed in *In-vitro* model [46]. However, coronavirus proteases, including $3CL^{pro}$, do not contain a C2-symmetric pocket, which is the target of HIV protease inhibitors, leading some to question the potency of HIV protease inhibitors in treating these viruses [47-48]. A recent study using *in vitro* and *in vivo* mouse models found stronger evidence

for anti-MERS-CoV activity for the antiviral drug remdesivir compared to lopinavir [48]. In order to determine the efficacy and safety of lopinavir/ritonavir for COVID-19, more adequately powered randomized clinical trials of lopinavir/ritonavir for COVID-19 are required [49].

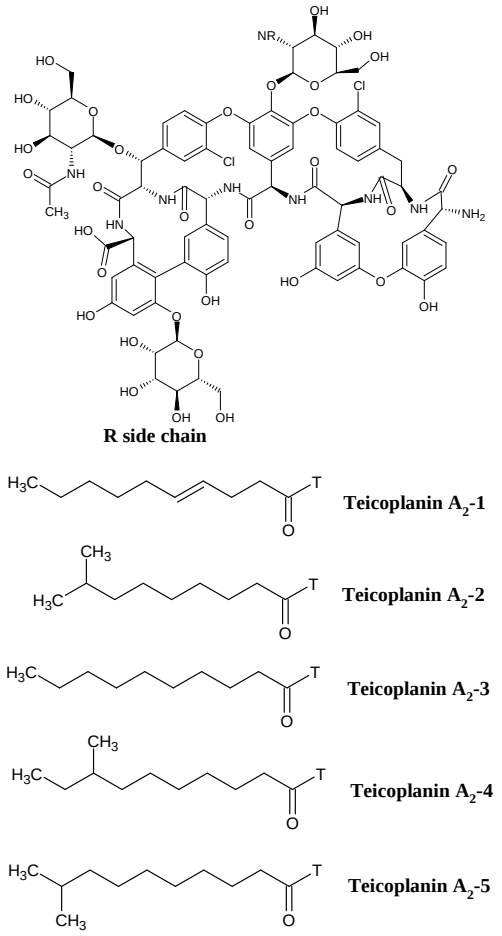

Figure 5: Structure of Teicoplanin.

Dosage regimen and duration: Despite the higher drug exposure compared with HIV-infected patients, the response of COVID-19 patients to antiviral treatment resulted in limited clinical value, arguing against the use of lopinavir/ritonavir in the clinical setting. Lopinavir/Ritonavir is still believed to be a valid therapeutic option for the treatment of COVID-19 and an investigation is warranted for a reduced dose (*i.e.* reduced to 400/100 mg daily perhaps) to improve drug tolerability [50].

Teicoplanin

Teicoplanin, a glycopeptide antibiotic routinely used to treat bacterial infections, was found to be active *in vitro* against SARS-CoV and has joined the list of molecules that could be used in the therapeutic arsenal against COVID-19 [43]. This antibiotic, currently used in the treatment of Gram-positive bacterial infections, especially staphylococcal infections, has already shown efficacy against various viruses such as Ebola virus, influenza virus, flavivirus, hepatitis C virus (HCV) and HIV as well as coronaviruses such as MERS-CoV and SARS-CoV [51,52]. A patent was filed use of teicoplanin in the treatment of infection caused by MERS-CoV in 2016 [53]. According to Zhou et al., in coronaviruses teicoplanin acts on an early stage of the viral life cycle by inhibiting the low-pH cleavage of the viral spike protein by cathepsin L in the late endosomes, thereby preventing the release of genomic viral RNA and continuation of the virus replication cycle [51]. A recent study by the same authors showed that this activity was conserved against SARS-CoV-2 (the target sequence that serves as the cleavage site for cathepsin L is conserved among SARS-CoV spike protein) [43]. The concentration of teicoplanin required to inhibit 50% of viruses (IC_{50}) *in vitro* was 1.66 μM, which is much lower than the concentration reached in human blood (8.78 μM for a daily dose of 400 mg) [43]. These preliminary results need to be confirmed in a randomized clinical trial. Based on of the reports for teicoplanin use in the treatment of infectious diseases further investigations on the antiviral effect in SARS-CoV-2 are required. Based on future outcomes it may be suggested as another potential alternative for the treatment of COVID-19 [54].

Brilacidin

Brilacidin (PMX-30063) is Innovation Pharmaceutical's lead Host defense Protein (HDP)/defensin-Mimetic drug candidate targeting SARS-CoV-2, the virus responsible for COVID-19. Laboratory testing conducted at a U.S. based Regional biocontainment Laboratory (RBL)

supports brilacidin's antiviral activity in directly inhibiting SARS-CoV-2 in cell-based assays. Additional pre-clinical and clinical data support brilacidin's therapeutic potential to inhibit the production of IL-6, IL-1β, TNF-α and other pro-inflammatory cytokines and chemokines (e.g. MCP-1), identified as central drivers in the worsening prognoses of COVID-19 patients.

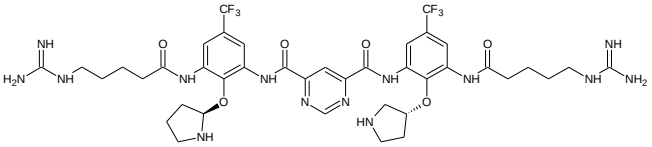

Figure 6: Structure of Brilacidin.

Brilacidin's antimicrobial properties might also help in fighting secondary bacterial infections, which can co-present in up to 20 percent of COVID-19 patients. Collectively, these data support Brilacidin as a promising and unique 3-in-1 combination i.e. antiviral, immune/anti-inflammatory, and antimicrobial candidate. Development of inhalant formulation might complement Brilacidin's anti-COVID-19 therapeutic potential. Brilacidin has been tested in multiple Phase 2 human trials for other clinical indications, providing an established safety and efficacy profile, thereby potentially enabling it to help confront the worldwide coronavirus crisis. During*In-vitro* experiment using VERO cells, Brilacidin has reduced the viral titer (load) of SARS-CoV-2 by 75 percent after only 1 hour of preincubation prior to the infection (10μM) as compared to vehicle control [55,56].

Solnatide

Solnatide is a synthetic peptide of less than 20 amino acids. This is the first compassionate use approved drug from Austria for the treatment of SARS-CoV-2-induced acute pulmonary dysfunction (ARDS) in mechanically ventilated COVID-19 patients in stage 6 and 7 on the WHO disease scale. Solnatide will be used to shorten the time of mechanical ventilation.

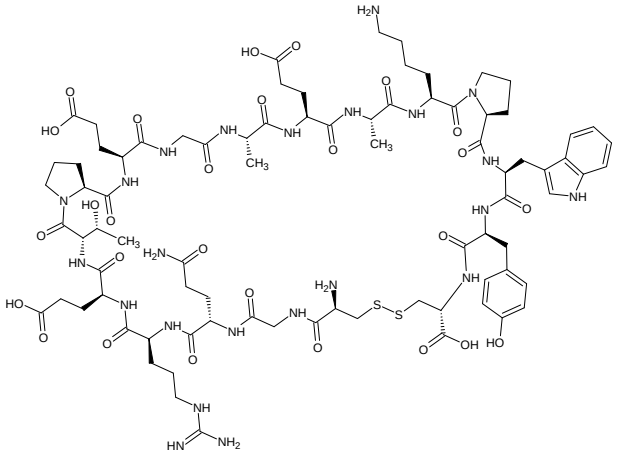

Figure 7: Structure of Solnatide.

Direct application of Solnatide in the lower airways in the form of a liquid aerosol is intended to activate the pulmonary sodium ion channels (ENaC) in order to directly activate alveolar fluid clearance and reduce the leakage of blood and fluids from the capillaries in the air space, i.e. accelerate the dissolution of alveolar oedema and reduce barrier damage in the lungs. In addition to alveolar fluid clearance activity, Solnatide inhibits the production of hypoxia-induced reactive oxygen species (ROS) and counteracts various ROS and toxin-mediated effects commonly observed in pneumonia. Solnatide inhibits PKC-alpha activation and thereby restores ENaC activity. The drug reduces the level of myosin light chain phosphorylation (MLC) and thus restores the barrier integrity of endothelial and epithelial cells. It has no pro-inflammatory activity and does not lead to increased production of chemokines or increased infiltration of neutrophils. Inhaled Solnatide has successfully completed the safety assessment of Phase-I and -II studies in mechanically ventilated ARDS patients with pulmonary oedema and a randomized, placebo-controlled pilot study in patients suffering from primary graft dysfunction following lung transplantation. A clinical trial is underway which will assess the local and systemic safety of 7 days orally inhaled sequential multiple ascending dosage (5mg, 60mg, 125mg) of solnatide in patients with pulmonary permeability oedema and moderate-to-severe ARDS [57,58].

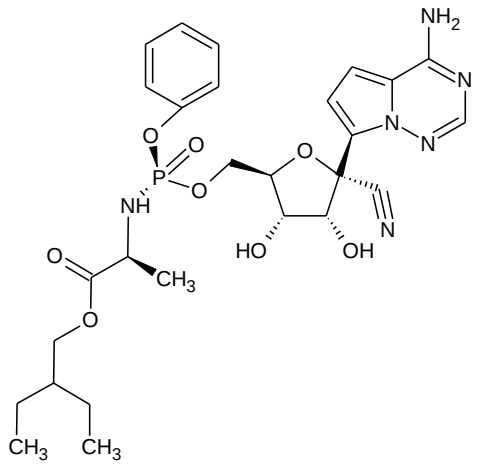

Figure 8: Structure of Remdesivir.

Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV) [48] infection in cultured cells, mice and non-human primate (NHP) models. It is currently under clinical development for the treatment of Ebola virus infection [59]. Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination [60]. A time-of addition assay has shown remdesivir functioned at a stage post virus entry, which is in agreement with its putative antiviral mechanism as a nucleotide analogue (EC_{90} = 1.76μM against 2019-nCoV in Vero E6 cells). The preliminary data supports role of remdesivir as inhibitor of viral infection efficiently in a human cell line (cancer Huh-7 cells), which is sensitive to 2019-nCoV [61].

Remidesivir

Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV) [48] infection in cultured cells, mice and non-human primate (NHP) models. It is currently under clinical development for the treatment of Ebola virus infection [59]. Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination [60]. A time-of addition assay has shown remdesivir functioned at a stage post virus entry, which is in agreement with its putative antiviral mechanism as a nucleotide analogue (EC_{90} = 1.76 μM against 2019-nCoV in Vero E6 cells). The preliminary data supports role of remdesivir as inhibitor of viral infection efficiently in a human cell line (cancer Huh-7 cells), which is sensitive to 2019-nCoV [61].

On 01 May 2020, the U.S. FDA issued an emergency use authorization for remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adults and children. Based on the evaluation of the emergency use authorization criteria and the scientific evidence available, it was determined that it is reasonable to believe that remdesivir may be effective in treating COVID-19. In the absence of adequate, approved, or available alternative treatments, the known and potential benefits of remdesivir to treat the infection caused by the life-threatening virus currently outweigh the known and potential risks associated with the drug [62].

A trial was conducted on hospitalized patients with COVID-19 and had radiologic evidence of pneumonia to compare the effects of remdesivir, at 5 and 10 days dose intervals. All of the patients were given 200mg of remdesivir on the first day, and 100 mg once daily on the following days. On day 14, the team assessed the clinical status of the patients. It is concluded from the trial that in patients with severe COVID-19 not requiring mechanical ventilation did not show a significant difference between a 5-day course and a 10-day course of remdesivir. To evaluate the benefits of current therapeutics a placebo control is necessary [63].

Meplazumab

CD147 is a novel identified receptor for SARS-CoV-2 infection. Meplazumab can efficiently inhibit the SARS-CoV-2 infection by targeting the CD147 in a dose dependent manner. All these results provide insights that CD147 acts as a functional entry receptor for SARS-

CoV-2, and serves as a therapeutic target for inhibiting virus infection [64].Meplazumab treatment accelerated the improvement in COVID-19, especially in the severe and critical cases. CD147 is a receptor for ligand CyPA, and its interaction with CD147 was key to the inflammation and chemotaxis [65]. CyPA is secreted in response to the inflammatory stimuli (e.g. viral infection), activates and attracts leukocytes via its receptor CD147 to the stimulus site [66]. The study demonstrated that anti-CD147 antibody could attenuate the chemotactic index of T cells induced by CyPA [67]. Multiple cytokines and chemokines were found to increase significantly in patients with COVID-19, which was significantly correlated with pulmonary inflammation index of chest CT imaging [1,68]. These results suggest that the excess immune cells migrating into lung tissue may cause uncontrolled immune response, leading to the inflammation storm, and aggravated disease. We presumed that meplazumab blocked the interaction between CyPA and CD147, attenuated the chemotactic effect of CyPA, decreased the immune cells in lung tissue, and facilitated the improvement of chest radiographic. Meplazumab, an anti-CD147 antibody, can block the host cell receptors to inhibit the virus invasion and replication by interrupting spike protein from recognizing CD147 receptor.

Lymphopenia was common in patients with COVID-19 and SARS patients, and can be used as an indicator of disease severity and prognosis [69]. Approximately 75.4% patients with COVID-19 reported lymphopenia [70]. In this trial, lymphocyte count in meplazumab-treated patients were restored in short time and CD147 is expressed on the activated T cells, [67] which may facilitate the invasion of SARS-CoV-2 to lymphocytes by binding spike protein, suggesting that CD147 may be involved in lymphocytopenia. Meplazumab interrupted this process by preventing virus invasion to keep lymphocytes survived. Second, the meplazumab blocks CD147-CyPA interaction and may contribute to lymphocyte elevation in peripheral blood by inhibiting the lymphocyte accumulation in pulmonary organ [71].

Dosage regimen and duration: Eligible patients were add-on administered 10 mg meplazumab intravenously at days 1, 2, and 5. Patients hospitalized in the same period were observed as concurrent control. 17 patients were enrolled and assigned to meplazumab group between Feb 3, 2020 and Feb 10, 2020. 11 hospitalized patients served as concurrent control. Baseline characteristics were generally balanced across the two groups. Compared to control group, meplazumab treatment significantly improved the discharged and case severity in critical and severe patients. Meplazumab efficiently improved the recovery of patients with SARS-CoV-2 pneumonia with a favorable safety profile. Our results support to carry out a large-scale investigation of meplazumab as a treatment for COVID-19 pneumonia [71].

Leronlimab

In critical and terminally-ill, COVID-19 patients profound elevation of plasma IL-6 and CCL5 (RANTES), decreased CD8+ T cell levels, and SARS-CoV-2 plasma viremia is reported. Following compassionate care treatment with the CCR5 blocking antibody leronlimab, we observed complete CCR5 receptor occupancy on macrophage and T cells, rapid reduction of plasma IL-6, restoration of the CD4/CD8 ratio, and a significant decrease in SARS-CoV-2 plasma viraemia. Consistent with reduction of plasma IL-6, single-cell RNA-sequencing revealed declines in transcriptomic myeloid cell clusters expressing IL-6 and interferon-related genes. These results demonstrate a novel approach to resolving unchecked inflammation, restoring immunologic deficiencies, and reducing SARS-CoV-2 plasma viral load via disruption of the CCL5-CCR5 axis, and support randomized clinical trials to assess clinical efficacy of leronlimab-mediated inhibition of CCR5 for COVID-19 [72].

Dosage regimen and duration

10 patients received a subcutaneous 700 mg dose of leronlimab after baseline blood collection and monitored longitudinally for 2 weeks after treatment. As early as 3 days after therapy, investigators noted a reduction of plasma IL-6, which returned to healthy levels by day 14. More variable levels, however, were observed with IL-1β, IL-8, and CCL5. There was a marked restoration in CD8+ T cell ratio in the blood following leronlimab treatment. However, investigators noted a decrease in SARS-CoV-2 plasma viraemia in all patients at day 7 following treatment, indicating that leronlimab may be effective in anti-viral immunity [73].

Darunavir and Cobicistat

Darunavir is a protease inhibitor marketed by Janssen and the anecdotal reports suggest potential of antiviral activity against COVID-19. It is, however, currently approved only for use with a boosting agent, and in combination with other antiretrovirals, for the treatment of HIV-1. Janssen has no in vitro or clinical data to support the use of darunavir as a treatment for COVID-19. The drug is in the process of being evaluated in vitro for any potential activity against the coronavirus [74].

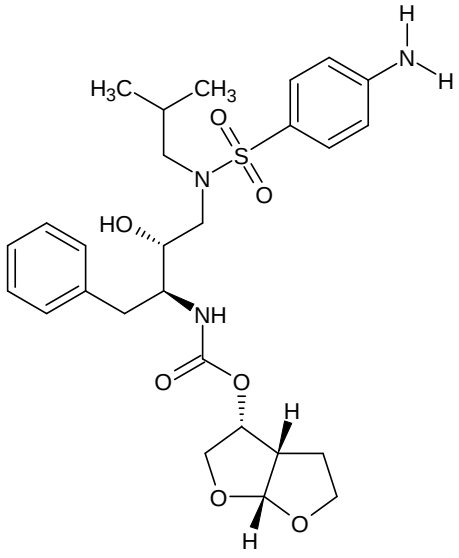

Figure 9: Structure of Darunavir.

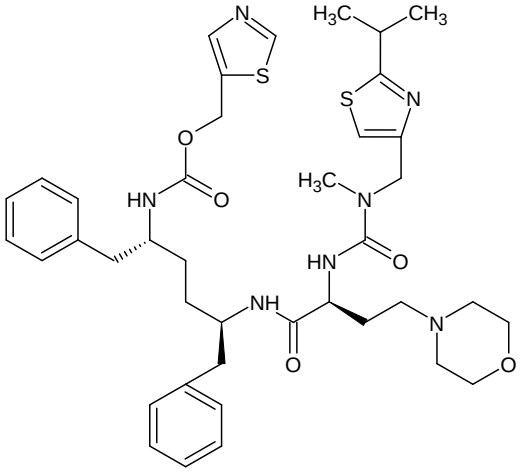

Figure 10: Structure of Cobicistat.

A pilot study was conducted by Jun Chen et al. among SARS-CoV-2 positive patients with an experiment group (15 patients, Darunavir/Cobicistat) and a control group (15 patients). Herein, participants in the experiment group received darunavir/cobicistat one pill (a single tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat) per day for 5 days while participants in the control group did not receive oral antiviral drugs.

The results were consistent found with the findings from a randomized controlled study which also failed to show the benefit of Lopinavir/Ritonavir treatment beyond standard care in hospitalized adult patients with severe Covid-19. In conclusion, this pilot study does not suggest that 5 days of darunavir/cobicistat could increase the proportion of negative conversion at day 7 than standard of care alone, although it was well tolerated [75].

Rintatolimod

Rintatolimod is a TLR-3 agonist (Poly I:Poly C12U; Ampligen; AIM ImmunoTech) (toll-like receptor 3 [TLR-3] agonist), broad spectrum antiviral agent is being tested as a potential treatment for COVID-19 by the National Institute of Infectious Diseases (NIID) in Japan and the University of Tokyo [76,77].

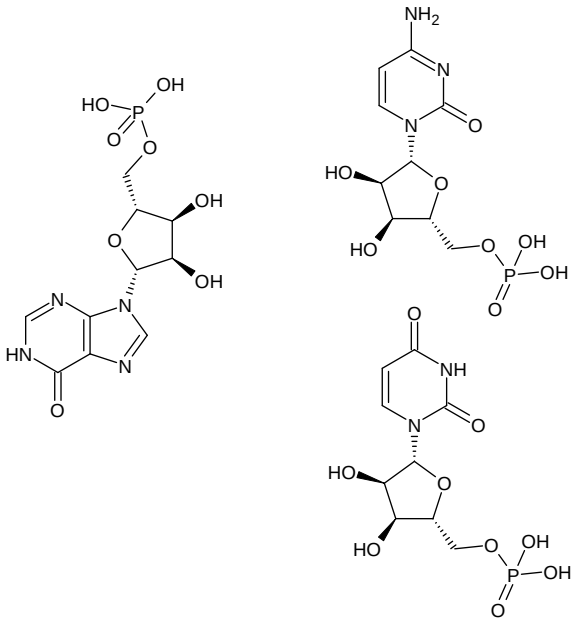

Figure 11: Structure of Rintatolimod.

Plitidepsin

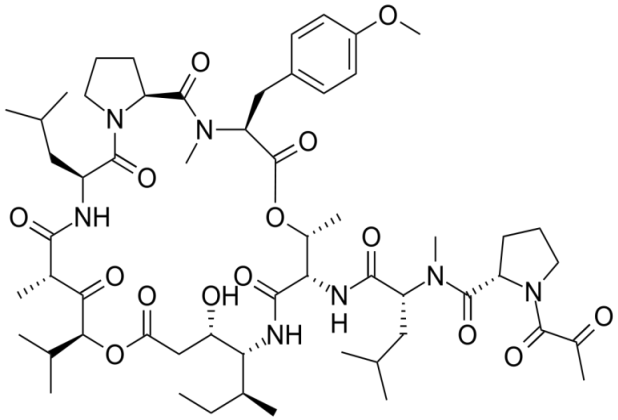

Figure 12: Structure of Plitidepsin.

Plitidepsin (Aplidin; PharmaMar) is a member of the compound class known as didemnins. In vitro studies from Spain report plitidepsin potentially targets EF1A, which is key to multiplication and spread of the virus. PharmaMar (MSE:PHM) reports that the in vitro studies results of Aplidin® (plitidepsin) on the human coronavirus HCoV-229E, which has a multiplication and propagation mechanism very similar to COVID-19, has been positive with a potency of the nanomolar order [78].

Favipiravir/Umifenovir

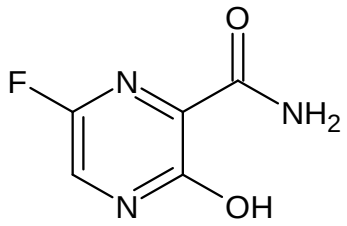

Figure 13: Structure of Favipiravir.

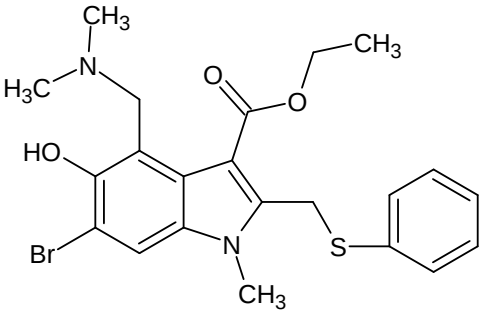

Figure 14: Structure of Umifenovir.

Glenmark Pharmaceuticals, a global pharmaceutical company, announced a new randomized, open-label study to test the combined efficacy of two antiviral drugs favipiravir and umifenovir as a potential COVID-19 treatment strategy. Favipiravir is an oral antiviral drug approved in Japan since 2014. It has a unique mechanism of action by which it inhibits viral replication. Umifenovir is another oral antiviral drug licensed for treatment and prophylaxis of influenza A and B infections in Russia and China. Umifenovir impedes the viral attachment to cells and acts as a viral entry inhibitor. Additionally it exhibits modulatory effects on the immune system and induces interferon-production. Hence combined use of favipiravir and umifenovir acting on different mechanisms offers a comprehensive antiviral cover on pre-entry and post-entry life-cycle of the SARS-CoV-2 virus. Both antivirals inhibited virus infection in vitro and have shown efficacy in COVID-19 clinical trials. The current Glenmark study will examine whether early administration of this combination, both acting by different mechanisms, enhances antiviral efficacy on COVID-19 patients.

The new combination clinical trial will be called FAITH-(favipiravir plus Um I fenovir (efficacy and safety) trial in Indian hospital setting). In the 158 hospitalized patients of moderate COVID-19 infection will be enrolled in the combination study and randomized in two groups: one group receiving favipiravir and umifenovir (with standard supportive care); and one group receiving Favipiravir along with standard supportive care. Patients in the arm receiving the drug will receive faviprivir 1800mg bid and umifenovir 800 mg bid on Day 1. Thereafter patients would receive faviprivir 800mg bid and umifenovir 800mg bid for the remaining course of the treatment. Duration of treatment will be 14 days. Simultaneously glenmark is conducting phase 3 clinical trials of favipiravir as a COVID-19 monotherapy option with 150 patients [79].

IFX-1

IFX-1 is a first-in-class antibody designed to target and blocks the activity of the complement activation C5a protein. This protein is part of the complement system- a set of more than 20 blood proteins that form part of the body's immune defences. InflaRx launched a Phase 2 trial to explore the potential of IFX-1 at treating patients with severe pneumonia associated with COVID-19. The trial will be divided into two parts, with an interim analysis to determine if it should proceed to a confirmatory phase [80].

CONCLUSION

Since the outbreak of global pandemic COVID-19 caused by SARS-CoV-2 various research labs are working on investigation of potential viral targets to control the spread and improve cure rate. The research efforts for last eight months since December 2019 has identified some important viral targets such as chemokine receptor CCR5, PLCγ-1, envelope protein, ENaC, membrane glycoprotein, nucleocapsid, protein kinase Cα, RdRp, surface glycoprotein, FASL receptor, toll like receptor 3, etc. The promising clinical outcomes with the current therapeutics i.e. repurposed drugs to vaccine will be useful to direct the current anti-COVID therapeutic research.

AUTHOR(S) CONTRIBUTION

All authors have contributed equally for the work and manuscript preparation.

ACKNOWLEDGEMENT

Authors SS and VMP will like to acknowledge the facilities and resources provided by KIET Group of Institutions, Delhi-NCR, India for the present work.

FUNDING

The work is not supported by any funding agency.

CONFLICT OF INTEREST

Authors declare no potential conflict of interest.

REFERENCES

1. Huang C, Wang Y, Li X, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506.
2. Wua YC, Chen CS, ChanYJ (2020) The outbreak of COVID-19: An overview. Journal of the Chinese Medical Association 83(3): 217-220.
3. Fouchier RM, Kuiken T, Schutten M, et al. (2020) Aetiology: Koch's postulates fulfilled for SARS virus. Nature423(6937): 240.
4. Perlman S (2020) Another decade, another coronavirus. The New England Journal of Medicine 382(8): 760-762
5. Peiris JM, Chu CM, Cheng VC, et al. (2003)Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: A prospective study. Lancet 361(9371): 1767-1772.

6. Zaki AM, Boheemen SV, Bestebroer TM, et al. (2012) Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. New England Journal of Medicine 367(19): 1814-1820.
7. Liu Y, Gayle AA, Smith AW, et al. (2020) The reproductive number of COVID-19 is higher compared to SARS coronavirus. Journal of Travel Medicine 27(2): taaa021.
8. Chen N, Zhou M, Dong X, et al. **(**2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 395(10223): 507-513.
9. Wang LS, Wang YR, Ye DW, et al. (2020) A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. International Journal of Antimicrobial Agents *55*(6): 105948.
10. Taiwan Centers for Disease Control (2020) *Severe Special Infectious Pneumonia*.
11. Zhu N, Zhang D, Wang W, et al. (2020) A novel coronavirus from patients with pneumonia in China, 2019. NewEngland Journal of Medicine 382(8): 727-733.
12. Rothe C, Schunk M, Sothmann P, et al. (2020) Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. New England Journal of Medicine 382(10): 970-971.
13. Holshue ML, DeBolt C, Lindquist S, et al. (2020) First case of 2019 novel coronavirus in the United States. The New England Journal of Medicine 382(10): 929-936.
14. Li Q, Guan X, Wu P, et al. (2020) Early transmission dynamics in Wuhan, China of novel coronavirus-infected pneumonia. The New England Journal of Medicine 382(13): 1199-1207.
15. Cheng ZJ, Shan J (2020) 2019 novel coronavirus: Where we are and what we know. Infection 48(2): 155-163.
16. Kampf G, Todt D, Pfaender S, et al. (2020) Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. Journal of Hospital Infection 104(3): 246-251.
17. World Health Organization (2020) Situation reports.
18. Chen H, Guo J, Wang C, et al. (2020) Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: A retrospective review of medical records. Lancet 395(10226): 809-815.
19. Wang D, Hu B, Hu C, et al. (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323(11): 1061-1069.
20. Xu XW, Wu XX, Jiang XG, et al. (2020) Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. The BMJ 368: m606.
21. Wang XF, Yuan J, Zheng YJ, et al. (2020) Clinical and epidemiological characteristics of 34 children with 2019 novel coronavirus infection in Shenzhen. Zhonghua Er Ke Za Zhi 58(0): E008.
22. (2020) Coronavirus Outbreak.
23. Chan JW, Yuan S, Kok KH, et al. (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 395: 514-523.
24. Jin YH, Cai L, Cheng ZS, et al. (2020) A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus [2019-nCoV] infected pneumonia. Military Medical Research 7(1): 4.
25. Chang D, Xu H, Rebaza A, et al. (2020) Protecting health-care workers from subclinical coronavirus infection. Lancet Respiratory Medicine 8(3): e13.
26. Li J, Li JJ, Xie X, et al. (2020) Game consumption and the 2019 novel coronavirus. Lancet Infectious Disease 20(3): 275-276.

27. https://www.who.int/health-topics/coronavirus#tab=tab_2.
28. Colson P, Rolain JM, Raoult D (2020) Chloroquine for the 2019 novel coronavirus SARS-CoV2. International Journal of Antimicrobial Agents*55*(3): 105923.
29. Colson P, Rolain JM, Lagier JC, et al. (2020) Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. International Journal of Antimicrobial Agents 55(4): 105932.
30. Chatre C, Roubille F, Vernhet H, et al. (2018) Cardiac complications attributed to chloroquine and hydroxychloroquine: A systematic review of the literature. Drug Safety 41(10): 919-931.
31. Gao J, Tian Z, Yang X (2020) Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Bio Science Trends14(1): 72-73.
32. Patil VM, Singhal S; Masand N (2020) A systematic review on use of aminoquinolines for the therapeutic management of COVID-19: Efficacy, safety and clinical trials. Life Sciences 254: 117775.
33. Savarino A, Boelaert JR, Cassone A, et al. (2003) Effects of chloroquine on viral infections: An old drug against today's diseases? Lancet Infectious Diseases 3(11): 722-727.
34. Cortegiani A, Ingoglia G, Ippolito M, et al. (2020) A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. Journal of Critical Care57: 279-283.
35. Yao X, Ye F, Zhang M et al. (2020) In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases 71(15): 732-739.
36. Retallack H, Lullo ED, Arias C, et al. (2016) Zika virus cell tropism in the developing human brain and inhibition by azithromycin. Proceedings of the National Academy of Sciences of the United States of America 113(50): 14408-14413.
37. Madrid PB, Panchal RG, Warren TK,et al. (2015) Evaluation of Ebola Virus Inhibitors for Drug Repurposing. ACS Infectious Diseases 1(7): 317-326.
38. Bosseboeuf E, Aubry M, Nhan T, et al. (2018) Azithromycin inhibits the replication of *zika virus*. Journal of Antivirals Antiretroviral 10(1): 6-11.
39. Bacharier LB, Guilbert TW, Mauger DT, et al. (2015) Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: A randomized clinical trial. JAMA314(19): 2034-2044.
40. Gautret P, Lagier JC, Parola P (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an openlabel non-randomized clinical trial. Journal of Antimicrobial Agents 56(1): 105949.
41. Karalis V, Ismailos G, Karatza E (2020) Chloroquine dosage regimens in patients with COVID-19: Safety risks and optimization using simulations. Safety Science 129: 104842.
42. (2020) AbbVie. Kaletra Prescribing Information.
43. Zhang J, Ma X, Yu F, et al. (2020) Teicoplanin potently blocks the cell entry of 2019-nCoV. bioRxiv.
44. Anand K, Ziebuhr J, Wadhwani P, et al. (2003) Coronavirus main proteinase (3CLpro) structure: Basis for design of anti-SARS drugs. Science 300(5626): 1763-1767.
45. Zhang L, Lin D, Sun X, et al. (2020) Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors. Science 368(6489): 409-412.

46. Choy KT, Wong AYL, Kaewpreedee P, et al. (2020) Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication *in vitro*. Antiviral Research 178: 104786.
47. Li G, Fan Y, Lai Y, (2020) Coronavirus infections and immune responses. Journal of Medical Virology 92(4): 424-432.
48. Sheahan TP, Sims AC, GrahamRL, et al. (2017) Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Science Translational Medicine 9(396): 3653.
49. Dorward J, Kome G (2020) Lopinavir/ritonavir: A rapid review of effectiveness in COVID-19.
50. Baldelli S, Corbellino M, Clementi E, et al. (2020) Lopinavir/ritonavir in COVID-19 patients: Maybe yes, but at what dose? Journal of Antimicrobial Chemotherapy 75(9): 2704-2706.
51. Zhou N, Pan T, Zhang J, et al. (2016) Glycopeptides antibiotics potently inhibit cathepsin L in the late endosome/lysosome and block the en-try of Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV). Journal of Biological Chemistry 291(17): 9218-9232.
52. Colson P, Raoult D (2016) Fighting viruses with antibiotics: An overlooked path. International Journal of Antimicrobial Agents 48(4): 349-352.
53. Pan T, Zhou N, Zhang H (2015) Use of teicoplanin anti-Middle East respiratory syndrome coronavirus. WIPO Patent.
54. Baron SA, DevauxC, Colson, P, et al. (2020) Teicoplanin: An alternative drug for the treatment of COVID-19? International Journal of Antimicrobial Agents 55(4): 105944.
55. Innovation Pharmaceuticals: Mechanism of action, pre/clinical data and academic literature supporting the development of brilacidin as a potential novel coronavirus (covid-19) treatment.
56. http://www.ipharminc.com/press-release/2020/5/19/innovation-pharmaceuticals-brilacidin-reduces-viral-titer-of-sars-cov-2-covid-19-by-75-percent-after-only-1-hour-of-preincubation-in-in-vitro-study-at-bsl-3-facility.
57. (2020) Covid-19: Solnatide approved for compassionate use. European Biotechnology.
58. https://clinicaltrials.gov/ct2/show/NCT03567577.
59. Mulangu S, Dodd LE, Davey RT, et al. (2019) A randomized, controlled trial of ebola virus disease therapeutics. The New England Journal of Medicine 381(24): 2293-2303.
60. Warren TK, Jordan R, Lo MK, et al. (2016) Therapeutic efficacy of the small molecule GS-5734 against ebola virus in rhesus monkeys. Nature 531(7594): 381-385**.**
61. Zhou P, Yang XL, Wang XG, et al. (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579(7798): 270-273.
62. Coronavirus (covid-19) update: FDA issues emergency use authorization for potential covid-19 treatment.
63. https://clinicaltrials.gov/ct2/show/NCT04292899.
64. Wang K, Chen W, Zhou YS, et al. (2020) SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. bioRxiv.
65. Yurchenko V, Constant S, Eisenmesser E, et al. (2010) Cyclophilin-CD147 interactions: a new target for anti-inflammatory therapeutics. Clinical and Experimental Immunology 160(3): 305-317.
66. Dawar FU, Wu J, Zhao L, et al. (2017) Updates in understanding the role of cyclophilin A in leukocyte chemotaxis. Journal of Leukocyte Biology 101(4): 823-826.

67. Lv M, Miao J, Zhao P, et al. (2018) CD147-mediated chemotaxis of CD4 (+) CD161 (+) T cells may contribute to local inflammation in rheumatoid arthritis. Clinical Rheumatology 37(1): 59-66.
68. Wu J, Wu X, Zeng W, et al. (2020) Chest CT findings in patients with corona virus disease 2019 and its relationship with clinical features.Investigative Radiology 55(5): 257-261.
69. Tan L, Wang Q, Zhang D, et al. (2020) Lymphopenia predicts disease severity of COVID-19: A descriptive and predictive study. Signal Transduction and Targeted Therapy 5(1): 33.
70. Guan WJ, Ni ZY; Hu Y, et al. (2020) Clinical characteristics of Coronavirus disease 2019 in China. The New England Journal of Medicine382: 1708-1720.
71. Bian H, Zheng ZH, Wei D, et al. (2020) Meplazumab treats COVID-19 pneumonia: An open-labeled, concurrent controlled add-on clinical trial. medRxiv.
72. Patterson BK, Seethamraju H, Dhody K, et al. (2020) Disruption of the ccl5/rantes-ccr5 pathway restores immune homeostasis and reduces plasma viral load in critical covid-19. medRxiv.
73. https://www.targetedonc.com/view/covid-19-death-toll-in-nyc-calls-attention-to-racial-disparities.
74. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses
75. Chen J, Xia L, Liu L, et al. (2020) Antiviral activity and safety of darunavir/cobicistat for treatment of covid-19.Open Forum Infectious Diseases7(7): ofaa241.
76. https://b2icontent.irpass.com/2265/180859.pdf.
77. https://aimimmuno.irpass.com/AIM-ImmunoTechs-Drug-Ampligen-to-Be-Tested-by-Japans-National-Institute-of-Infectious-Diseases-as-a-Potential-Treatment-for-the-New-SARS-Coronavirus-SARS-CoV-2-Responsible-for-the-New-Human-Infectious.
78. pharmamar.com/wp-content/uploads/2020/03/PR_Results_Aplidin_coronavirus.pdf.
79. https://www.prnewswire.com/in/news-releases/glenmark-to-commence-new-phase-3-clinical-trial-on-combination-of-two-anti-viral-drugs-favipiravir-and-umifenovir-in-hospitalized-patients-of-moderate-covid-19-in-india-836904730.html.
80. https://ancavasculitisnews.com/2020/06/01/first-part-phase-2-ifx-1-trial-aav-patients-eu-fully-enrolled-inflarx-says/.