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Epidemiology, Pathogenesis, Diagnosis and Treatment Options of Covid-19: Evidence and Experience

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Abstract

The new coronavirus infection (COVID-19) outbreak that started in China in December 2019, spread rapidly over the world and causes a major worldwide tragedy. Much like the coronavirus that causes SARS, SARS-CoV-2 infection causes clusters of severe respiratory disease. The most common form of transmission is droplet from human-to-human transmission, contaminated hands and surfaces with incubation durations varying from two to fourteen days. Till now there is no effective medication available in the prevention and treatment of covid-19 except isolation and vaccine. However, clinicians repurpose certain medication on the basis of sign and symptoms of infections. The objective of this article is to explore the trials that have been conducted for the development of established or new antiviral drugs, repurpose drugs, vaccine, and drugs under clinical trial for the prevention and management of COVID-19.

Keywords: COVID-19, antiviral drugs, repurposed drugs, vaccine, clinical trial.

Introduction

There has been an outbreak of a new coronavirus strain (COVID-19). Wuhan, China, spread all over the globe. A virus that causes serious respiratory infections in humans, COVID-19, has been declared a global health threat by the World Health Organization (WHO). Since 2003, 2012, and late 2019, three previously unknown coronaviruses (SARS-CoV, MERS-CoV, and 2019-nCoV, later called SARS-CoV-2) have emerged and spread worldwide. As part of the Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE), a group of independent experts monitors and evaluates the evolution of SARS-CoV-2 to assess whether individual mutations or combinations of mutations alter the behavior of the virus. The TAG-VE convened on 26 November 2021 to determine the status of SARS-CoV-2 variant B.1.1.529 (omicron). The South African government notified WHO of the variant B.1.1.529 on 24 November 2021. RNA viruses encased in encasings called Coronaviruses infect animals and birds and cause a variety of diseases (1). SARS-CoV-2 is a new Coronaviridae member that is unrelated to SARS-CoV or MERS-CoV, according to phylogenetic analysis. (2, 3). Although SARS-CoV-2 exhibits a 96.3 percent genetic similarity to RaTG13, a bat coronavirus discovered in Yunnan in 2013, bats were not the virus's primary source (4). Coronaviruses, such as HCOV-229E, HCOV-NL63, HCOV-OC43, and HCOV-HKU1, cause moderate upper respiratory infections in between 15% and 30% of all cases of the common cold. The first SARS case was reported in Guangdong in 2002, and the virus killed 744 people before it was eradicated in 2003. MERS was first identified in Saudi Arabia in 2012, and it has since spread throughout the world, causing 2494 cases and 858 deaths (7). In January

2020, SARS-CoV-2, a novel coronavirus that causes coronavirus disease-2019, was found in Wuhan, China (COVID-19). (8). Report found that at the end of January 2022, 315,345,967 people had died as a result of the global pandemic (9). The most common sign and symptoms of these infections are fever, dry cough, fatigue, and anosmia. In addition, in 80% of cases, the condition affects upper airways and a small portion of lung tissue, in 15% of cases; dyspnea, tachypnea, hypoxemia, cardiovascular symptoms, and broad lung damage are all signs of severe infection. An infection can worsen by acute respiratory distress syndrome (ARDS) or disseminated intravascular coagulopathy (DIC) in about 5% of patients, resulting in respiratory failure, septic shock, and multisystem organ dysfunction (10-12). A lot of research has been done to develop vaccines and therapeutic drugs because there are no viable treatments for coronavirus infections. As of October 22, 2020, remdesivir, a broad spectrum antiviral medicine, was approved by the FDA for the treatment of moderate or severe COVID-19 in hospitalized patients aged 12 and up, and the objective is to shorten the time of recovery. Further, two pharmaceutical companies are developing COVID-19 vaccines that are up to 95% effective as of November 2020 (13-15). In addition to these medications, COVID-19 is often treated with supportive measures. In patients with respiratory distress or failure, noninvasive positive pressure ventilation and mechanical ventilation, along with supplementary oxygen, may be necessary (16). In addition to COVID-19, corticosteroids like methylprednisolone have been shown promising effect in the modulation of host immunity (17, 18). During this study, all aspects of COVID-19 infection are examined, including epidemiology, molecular biology, pathophysiology, diagnosis, isolation, and treatment.

Epidemiology:

The global pandemic had resulted in 315,345,967 confirmed infections and 5,510,174 fatalities as of January 2022, resulting in a fatality rate of roughly 2% (315,345,967/5,510,174).According to a study of early transmission dynamics, COVID-19 incubation time was 5.2 days on average (95 % confidence interval [CI], 4.1-7.0), with the 95th percentile of the distribution at 12.5 days (19). Another study examined the travel history and onset of symptoms in 88 confirmed cases and discovered a 6.4-day incubation period (95 percent confidence interval: 5.6-7.7). (20). There was also a case that had a 19-day incubation period (21). Longer incubation times, for example, need alterations in screening and control policies (22). According to specialists, a 19-day incubation period is a low-probability event, hence a 14-day quarantine period is advised. The World Health Organization divides COVID-19 patients into four categories: mild, moderate, severe, and critical. Mild cases meet clinical and epidemiological criteria but don't show any signs or symptoms of viral pneumonia or hypoxia. Pneumonia is a symptom of a relatively minor ailment. Severe sickness is defined as pneumonia or respiratory distress with a breathing rate of 30 breaths per minute or higher. Critical sickness is defined as an acute pneumonia that has been made worse by the advent of ARDS, sepsis, or septic shock (23). The majority of COVID-19-infected people will have mild to moderate symptoms (80.9%), with 13.8 percent having severe sickness and 5% having an emergency (24). Patients with COPD, diabetes, cerebrovascular disease, coronary heart disease, hypertension, and cancer had a higher risk of developing severe illness or being admitted to the ICU when compared to non-severe COVID-19 patients (25). According to the most recent study analyzing smoking status in COVID-19 patients, current smokers and patients with a smoking history have a higher risk of developing severe or critical COVID-19 and requiring mechanical ventilation (26). A small research of COVID-19-isolated people found a connection between viral RNA on ambient surfaces and airflow-induced droplet deposition. The virus was also found in sewage, toilet bowl, and sink samples, indicating viral shedding in faeces (27). Coughing and sneezing produce huge respiratory droplets (>5 mm), but exhaling and normal speech release little aerosols (5 mm) (28). In a study examining the efficacy of facemasks in preventing respiratory virus transmission, the virus was found only in samples of respiratory droplets and aerosols collected from participants who weren't wearing them (29).

Molecular biology:

SARS-CoV, MERS-CoV, and SARS-CoV-2 are all members of the Coronaviridae family, and the genome analysis have shown 27 to 32 kilobases with single-stranded positive-strand RNA genome (30, 31). The severe acute respiratory syndrome coronavirus 2 is identified by its trimeric S glycoproteins on the pleomorphic (round or oval) outer membrane (SARS-CoV-2). M and E are transmembrane structural proteins present in the viral envelope, while N or nucleocapsidis a multifunctional protein found in the viral DNA whichplay major role in the survival (32, 33). Some of these proteins are glycosylated in the Golgi apparatus, which results in the formation of glycoproteins. The spike (S) glycoprotein is the most conserved protein, which is very important for the receptor recognition, virus's attachment to host cells, facilitate membrane fusion, and entry of virus particle into host cell, is the most likely therapeutic target among all structural proteins. When S protein is primed by the host cell serine protease known as TMPRSS2, the cellular receptor recognizes it (34). Similarly, protease also primes the SARS-CoV-2entry receptor is angiotensin-converting enzyme 2 (ACE2). The ACE2 receptor is located on bronchial apical surface of epithelial cells, mucosal cells of lungs and intestine, and alveolar type II pneumocytes. When the virus's spike-like S proteins are interacted due to electrostatic forces and bind to the receptor-binding domain (RBD) of the host S glycoprotein, results highly conserved RBD-ACE-2 complex which causes large-scale conformational changes at S1/S2 in the S protein, allowing the virus to enter the cell cytoplasm and provides insight into viral transmission and multiplication (35, 36).Report found that despite irregular transcription process, this SARS-CoV-2 viruses replicates in a continuous manner like that of other coronaviruses(37). The process continuous process of replication of SARS CoV-2 occurred with the help of S-protein in the epithelial tissue of respiratory tract, especially at the nasal cavity, where the initial sign of mild clinical symptoms like loss of smell was found to be occur in affected patients (38). However, when the progression of replication of virus is more severe, then it's spread to the lower part of respiratory tract like lungs airway and causes moderate to severe pulmonary illness along with other tissue abnormalities including neurological, cardiovascular, gastrointestinal, and central nervous system dysfunctions (39). Further, the progress of disease affect the immune cells of spleen and lymph nodes as well as CD169 macrophages, can act as viral carriers, maintaining viral load and facilitating tissue dispersion. Genomic reports cited that the mutation in the sequence code of S1 protein of SARS-CoV-2 results enhanced infections and tissue damage (40).As per the report of World Health Organization (WHO), the most common signs and symptoms of SARS-CoV-2 infections are fever and cough, however, the other symptoms like tiredness, myalgia, sore throat, and diarrheamight be take place in some individuals (41). In addition, atypical symptoms such as neurological abnormalities, GI disturbance, and cardiovascular disorder also involved with this infections (42). A meta-analysis clinical trial shows that COVID-19 patients, fever and dyspnea were the critical indicators of disease severity and progression, decides the patient's status of admission into ICU or non-ICU (43).The screening and testing of person who has had contact with a COVID-19 affected patients, key indicator of diagnosis. In this regards, WHO recommends and suggests first priority of testing to the most vulnerable healthcare worker those who has chance of reinfection is high or travelled to COVID-19 impacted nations or sickness persons (44, 45, 46). The diagnostic test includes serology or hematology test, and sometimes chest CT scanning depending on the patients sign and symptoms (46). However, genomic analysis known as nucleic acid amplification test (NAAC) was conducted to identify the sequence code of viral RNA (47). In addition, reverse transcriptase polymerase chain reaction (Rt-PCR) and real time Rt-PCR were the most sophisticated technique used to identify the SARS-CoV-2 genes instantly (48). Now a days, there are three new types of diagnosis tools are available which can directly measure and quantify the COVID-19 genes includes nucleocapsid (N), spike (S) and helicase enzymes (49). Among them, the in vitro, Hel test had the lowest limit of detection of the three new assays, implying that extremely sensitive and specific tests could aid in COVID-19 laboratory diagnosis (50). Despite the fact that RT-PCR testing can detect SARS-CoV-2, false-negative results can occur in 20% to 67 percent of patients due to the

testing's quality and timeliness, as PCR positive is found during the early stages of symptoms (51). The viral load in the upper respiratory tract (URT) peaks around the time symptoms develop, and viral shedding occurs 2-3 days prior. Because there is a substantial probability of false-negative results, clinical, laboratory, and imaging data are used to make a provisional diagnosis (52). A wide range of equipment and trained analysts are required for quantitative polymerase chain reaction (qPCR) analysis, which are readily available at well-established laboratories for improved viral genome sequencing (53). Despite negative RT-PCR results, typical chest computed tomography (CT) scan is a most maindevice which used X-ray beam for fast diagnosis of fever, sore throat, fatigue, coughing, or dyspnea who have recently been exposed to COVID-19, the most important application is observation of bilateral ground glass and pulmonary opacities with rounded shapes and peripheral distribution, indicating that it could be useful for progression of diseases (54).However, hematological test includes D-dimer, serum test, and lymphopenia play vital role in the diagnosis of disease severity those who had admitted in hospital with cases of pneumonia. Systematic review report of 19 studies comprising 2874 hospitalized patients in China shows more than 88 percent of hematological disorder involving pneumonia, suggest that haematological tests could be strong indicator for severity of theCOVID-19 infection (55, 56). Therefore, both imaging and clinical hematological diagnosis tool might be help in the early detection of COVID-19 pneumonia along with other abnormalities.

Treatment options

FDA as well as WHOhas approved the following medication for the management of COVID-19 infection on the basis of disease sign, symptoms and severity of cases.

Remdesivir (RDV)

RDV is an analogue of 1'-cyanoadenosine nucleotide, oldest antiviral drug, recently got approval by FDA on 22nd October 2020 for the management of COVID-19 infections (57). The drug RDV triphosphate, interacted efficiently (3.65 fold) than endogenous ATP with COVID-19 RdRp complex and hence able to prevent genomic replication by preventing RNA dependent RNA polymerase (RdRp). In addition, the in vitro experiment has confirmed that the presence of 1'-cyano group of RDV exhibits steric interaction with Ser-861 of RdRp results chain termination at i+4 point, consequently the inhibition of translocation and replication process and produces broad antiviral action against variety of viral family such as SARS and MARS (58). Clinical reports stated that RDV shows effective action against mild to severe SARS-CoV-2 infections in both adults and children with more than 12 year of age as well hospitalized patients (59). One of the report of United States found that RDV at 100 mg in injection form successfully treated the COVID-19 pneumonia symptoms on the 7th days of hospital admission (60). However, despite of effective antiviral effect, it has certain adverse effect of GI-disturbance, rectal bleeding, liver damage (61).

Favipiravir (FPV)

Like remdesivir, FPV is also a nucleoside analogue, act by selectively inhibit the RdRp enzymes. After administration of FPV, it became phosphorylated intracellularlly into more active FPV-ribofuranosyl-5'-triphosphate which act as viral substrate and interacted with RNA strand results inhibition of RdRp enzymes, consequently termination of viral protein synthesis (62). The above mentioned antiviral mechanism suggests the potential use of FPV against many virus including SARS-CoV-2, influenza A, B, and C viruses. It was found that the clinical dose of 1600 mg and 600 mg were available in the management of SARS-CoV-2 infections of Chinese people (63).

Molnupiravir (MPV)

MPV is a ribonucleosideanalogue, available as a prodrug namely β-D-N4-hydroxycytidine (NHC) shows wide spectrum antiviral action against various RNA viruses including SARS-CoV-2 (64, 65). The possible mechanism of antiviral action of MPV is based on inhibition of RdRp enzymes that prevents viral replication. As the active NHC is structurally similar to viral cytidine and hence interacted selectively with viral RNA strand and results inhibition (66). Clinical report demonstrated that MPV has shown significant effect in the reduction of risk of mortality in hospitalized COVID-19 patients (67). However, the certain

condition is recommended by European Medicines Agency for the use of MPV like patients must be adult COVID-19 who do not require supplemental oxygen and who have a greater risk of developing severe COVID-19. The medication should be administered no later than five days after the onset of symptoms (68).

Lopinavir/Ritonavir (LPV/RTV)

LPV/RTV are the potential protease inhibitors (PI) used to treat HIV infections. The combination of LPV/TRV in the dose of 200/50 mg was used applied in the management of hospitalized COVID-19 patients (69), confirmed by the randomized controlled clinical trial study. Another clinical trial conducted by the Chinese team involving 99 COVID-19 patients admitted in hospital with less than 94% of oxygen saturation received LPV/RTV (400/100 mg) for the period of 14 days, results shows no significant improvement in clinical symptoms than standard care. However, GI disturbance was found to be the common adverse effect of these treatment regimen. The molecular mechanism of antiviral action of LPV/RTV based on interference of the functions of 3-chymotrypsin protease (3CLpro) enzyme which helps in the expression of viral RNA and protease formation, results inhibition of viral replication and release from the host cell (70).

Nirmatrelvir (NTV)

Similarly, another Pfizer based investigational protease inhibitor NTV has been shown significant result in the reduction of risk of COVID-19 illness. The possible mechanism of NTV is inhibition of COVID-19 infection by interfering the synthesis of main protease (Mpro) results down regulation of process of translated polyprotein chain from the viral RNA consequently prevention of viral replication (71). This mechanism is confirmed using X-ray crystallography results with Ki =3.1 nM and its IC50=19.2 nM inhibited recombinant SARS-CoV-2 Mpro, suggests NTV is a potential agent in the management of SAR-CoV-2 infections. Further the combination of NTV with RTV was studied against SARS-CoV-2, results shows potentiation effect of NTV in the inhibition of protease as RTV increase the plasma concentration of NTV by preventing oxidative metabolic process of CYP3A (71). Randomized trial involving 2246 COVID-19 participant with symptoms of severe illness, when started treatment of NTV within 3 days of onset of symptoms, results indicate 89% reduction rate of risk of mortality with less adverse effect in compared to placebo group (72), suggesting NTV could be future promising agent in the management of COVID-19 infections.

Chloroquine, Hydroxychloroquine, and Azithromycin

The weak bases antimalarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ) repurposed for the management of COVID-19 infections of asymptomatic, mild non-hospitalized and hospitalized patients. The rational for the selection of these antimalarial drugs in COVID-19 is increases endosomal pH from 4.5 to 6.5, results prevention of fusion between virus and host cell membrane (73). In addition, the CQ prevents binding of virus to ACE-2 receptor by inhibiting the glycosylation of the spike protein of the respiratory cellular receptor(74). Report found that CQ or HCQ has the potential ability to bind with gangliosides and sialic acids which prevents the interaction of S protein of virus and the ACE-2 receptor on host cell surface, results prevention of viral genome release (75). Similarly, Azithromycin is the macrocyclic antibiotics used in the management of COVID-19 infections because of its antiviral and anti-inflammatory properties. Molecular modeling demonstrated that when azithromycin combined with CQ or HCQ, shows synergistic in vitro potential against SARS-CoV-2 (76). However, several clinical trial reports including RECOVERY, PETAL, ATOMIC-2 shows no such significant result in the recovery when used in hospitalized patients, therefore FDA has not approved these three medication for the management COVID-19.

Interleukin (IL)-6 inhibitor

There are two important IL-6 inhibitors likeSarilumab and Tocilizumab have shown promising result in the treatment of COVID-19. Reports found that the level of proinflammatory cytokine (IL-6) concentration in blood increased in COVID-19 patients, and which play a key role in cytokine storm as well as acute inflammation (sepsis), respiratory failure, immune dysregulation.In this context, Sarilumab and Tocilizumabexhibited

significant effect in the oxygen transfer from lungs to blood and improves respiratory functions in COVID-19 patients. Additionally, both these IL-6 inhibitors modulates immune function and makes the patient healthier. Most important advantages of these medication is low adverse effect so that patients'compatibility is more than others (77).

Convalescent plasma

Convalescent plasma (CP) or blood plasma obtained from recovered patient who have infected with an infection. CP has been used as effective therapy in the management of different infectious disease includes COVID-19. The possible mechanism action of CP is neutralization of infectious agent through generating antibodies (78). Additionally, the therapeutic effect of CP in COVID-19 is based on the activation of complement system, reverse inflammation cascade, and suppression of cytokines which leads to prevention of cytokine storm (79). Recently, CP has gain more attention because it produces passive administration of antibody to COVID-19 (79). However, the random clinical trial report has not been established the effectiveness of CP in clinical use, hence future study is required in the treatment of infectious disease.

Monoclonal antibodies

The monoclonal antibodies (MAB) are the laboratory based protein molecules that behaves like human antibodies and modify the host immune system during infectious disease including SARS-CoV-2 infection. MAB shows most promising treatment option in the management of mild to moderate SARS-CoV-2 symptoms. Recently, FDA and WHO recommends certain MBAs like for the effective management of COVID-19 symptoms.

Casirivimab/Imdevimab

In patients with COVID-19 infection at high risk of progressing to severe COVID-19 and hospitalisation, the combination of neutralizing monoclonal antibodies casirivimab and imdevimab is conditionally recommended by the WHO (80). Furthermore, it is recommended for patients with severe or critical COVID-19, provided the patient is seronegative. An intravenous infusion or four subcutaneous injections may be used to administer this combination. This combination of neutralizing monoclonal antibodies was recommended by the European Medicines Agency (EMA) for use in the EU in November 2021 as treatment of confirmed COVID-19 in adults and adolescents (over 12 years old and weighing at least 40 kg) who do not require supplemental oxygen and who are at a high risk of the disease progressing to severe COVID-19 (81).The FDA also issued an 'Emergency Use Authorization' in November 2021 (82).The antigen of Imdevimab, a recombinant monoclonal antibody to SARS-CoV-2 spike protein, is human immunoglobulin G1 (IgG1). SARS-CoV-2 can't attach to the human ACE2 receptor owing to the binding of the S1 subunit of the spike protein receptor-binding domain (RBD). By preventing viral binding to the host cell, this decreases viral load by preventing entry and replication. Caserivimab binds to a region of the spike protein RBD that is not overlapping with imdevimab, and its combination is thought to reduce viral mutations. Furthermore, the combination of the two drugs had retained activity against variants of SARS-CoV-2 (83-85) such as B.1.1.7 (UK), B.1.351 (South Africa), P.1 (Brazil), and B.1.427/B.1.429 (California).

Bamlanivimab/Etesevimab:

In a phase 3 trial, researchers examined bamlanivimab and etesevimab in an ambulatory COVID-19 patient population with mild or moderate disease and a high risk of developing severe disease. Compared to the placebo group, only 11 (2%) of those in the bamlanivimab-etesevimab group were hospitalized or died on Day 29 (absolute difference = 4.8%; 95 percent CI: *7.2 to *2.2; relative risk difference: 70%; P=0.001). After seven days, patients who received bamlanivimab with etesevimab showed greater reduction in log viral load from baseline than those who received a placebo (difference from placebo was 1.20; 95 % CI: 1.46, 0.94; P*0.001) (86). The effectiveness of bamlanivimab for preventing transmission of COVID-19 in long-term care facility residents was also tested in a phase 3 trial (BLAZE-2) (87). There was no statistically significant difference between the placebo and bamlanivimab groups after eight weeks of follow-up (OR 0.43; p0.001). Furthermore, mutations reported in developing disease strains, like as the E484K mutation found in

B.1.351 and P.1, have been linked to SARS-CoV-2 resistance to monoclonal antibodies like bamlanivimab in vitro (88). The EMA has paused its rolling review of bamlanivimab and etesevimab as a result of Eli Lilly Netherlands BV's withdrawal from the process (89).

The antiviral bamlanivimab is a monoclonal antibody (mAb) that neutralizes human IgG1k and targets spiking protein of SARS-CoV-2 and is unmodified at the Fc region. For spike protein attachment to the human ACE2 receptor, bamlanivimab's binding constant is 0.071 nM, and its IC50 value is 0.17 nM (0.25 g/mL). Etsesevimab neutralizes human IgG1k mAb to SARS-CoV-2 by substituting amino acids in the Fc region (L234A, L235A). Etesevimab has a dissociation constant (KD) of 6.45 nM and an IC50 of 0.32 nM in the presence of spike protein (0.046 g/mL) for attachment to human ACE2 receptors. The receptor-binding domain (RBD) of the S-protein binds both etesevimab and bamlanivimab. Use of both antibodies at the same time reduces the risk of viral resistance (90).

Sotrovimab:

GlaxoSmithKline PLC and VirBiotechnology Inc. presented the interim analysis of a phase 3 clinical trial of the monoclonal antibody sotrovimab (VIR-7831) for the treatment of mild-to-moderate COVID-19 in patients at high risk of hospitalisation on March 26, 2021. Researchers discovered that when compared to placebo, sotrovimab reduced hospitalizations or fatalities by 85 percent (p=0.002). Sotrovimab has received an emergency use authorization from the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) has recommended it for the treatment of COVID-19 when administered to adults and adolescents >12 years of age and weighing at least 40 kilograms who do not require supplemental oxygen therapy and are at risk of developing severe COVID-19c (91, 92).

SARS-CoV-2, the virus that causes COVID-19, is caused by a recombinant human IgG1k monoclonal antibody called Sotrovimab that targets an epitope of its spike protein receptor-binding domain. This conserved epitope discourages the development of viral resistance to the antibody (93). SARS-CoV-2 cannot bind to the spike protein, which prevents it from entering human cells (94). This compound does not interfere with the binding of human ACE2 receptors, and instead inhibits an undefined step that occurs after viral infection and before fusion of viral to cell membranes. Sotrovimab (LS modification) has a longer half-life because amino acids have been substituted in its Fc component.

Tixagevimab/Cilgavimab:

The combination of tixagevimab (AZD8895) and cilgavimab (AZD1061) (95) has been approved for use as a prophylactic treatment for symptomatic COVID-19 infections by AstraZeneca's AZD7442. AZD7442 significantly reduced symptoms of COVID-19 compared to a placebo in a phase 3 multicenter, double-blind, placebo-controlled trial (PROVENT) (96).

The SARS-CoV-2 enters cells when the host cell ACE2 (angiotensin-converting enzyme 2) is active. The S1 subunit of a trimeric glycoprotein binds to ACE2 through its receptor-binding domain (RBD), while the S2 subunit assists in fusion following the removal of the S1 subunit (97,98). Using large groups of B cells recovered from SARS-CoV-2 infection, large-scale screens showed that the most powerful neutralizing antibodies bound to the RBD of S1 and disrupted its interaction with human ACE2 (98). In order to prolong the half-life and reduce antibody effects, specific amino acids were replaced in cilgavimab to reduce the effect of antibodies and thereby develop a recombinant monoclonal antibody for human IgG1k (99). Like tixagevimab, ilgavimab binds to a non-overlapping region of the S1 RBD and binds both the "down" and "up" versions of the S protein at a KD of 14.0 pM (100). Based on various cell culture experiments, it appears to prevent antibody-dependent cell death (ADCD), phagocytosis (ADCP), or natural killer cell activation (ADNKA), suggesting that its protective effect is responsible for blocking the RBD-ACE2 interaction. A cellular assay showed that ilgavmiab inhibited RBD-ACE2 binding by an IC50 of 0.53 nM(80 ng/mL) and neutralized SARS-CoV-2 (strain USA-WA1/2020) by an EC50 of 211.5 pM (32 ng/mL) (99).

Regdanvimab:

The European Medicines Agency (EMA) approved regdanvimab on 11 November 2021

for use in adults with COVID-19 who are at high risk of severe disease but do not require oxygen supplementation (101). A Phase 3 clinical trial evaluating regdanvimab's efficacy and safety involved more than 1315 participants across 13 countries, including Romania, Spain, and the United States. Regdanvimab significantly reduced the risk of hospitalization or death related to COVID-19 by 72% for patients at high risk of progressing to severe disease, and by 70% for all patients (102).

Regdanvimab is a human IgG1 recombinant antibody that binds to the receptor-binding domain of the spike protein of CoV-2 SARS (103, 104). Regdanvimab prevents cellular entry of SARS-CoV-2 and subsequent replication by blocking this interaction. Spike proteins and angiotensin-converting enzyme 2 (ACE2) receptors work together to promote viral entry into host cells.Regdanvimab appears to bind to spike protein RBD exclusively in its "up" conformation, whereas most other antibodies to ACE2 block the spike protein in a different way (105).

Vaccines:

The WHO has validated several COVID-19 vaccines for use in emergencies (Emergency Use Listing). The first mass vaccination campaign began in December 2020.Through the WHO Emergency Use Listing process, a product is evaluated on the basis of all the available safety and efficacy data, as well as its suitability for use in low- and middle-income countries.The following vaccines have obtained EUL as of January 2022:

- The Pfizer/BioNTechComirnaty vaccine, 31 December 2020.
- The SII/COVISHIELD and AstraZeneca/AZD1222 vaccines, 16 February 2021.
- The Janssen/Ad26.COV 2.S vaccine developed by Johnson & Johnson, 12 March 2021.
- The Moderna COVID-19 vaccine (mRNA 1273), 30 April 2021.
- The Sinopharm COVID-19 vaccine, 7 May 2021.
- The Sinovac-CoronaVac vaccine, 1 June 2021.
- The Bharat Biotech BBV152 COVAXIN vaccine, 3 November 2021.
- The Covovax (NVX-CoV2373) vaccine, 17 December 2021.
- The Nuvaxovid (NVX-CoV2373) vaccine, 20 December 2021

Table: 1: Details of clinical trials related to covid-19

SL No.	Title of the Trial	Drug name	Status	Population	Phase
1	DAS181 for Severe COVID-19: Compassionate Use	DAS181	Completed	Enrollment-04 (18 year-70 year age group)	NA
2	Clinical Trial to Evaluate the Effectiveness and Safety of Tocilizumab for Treating Patients With COVID-19 Pneumonia	Tocilizumab	Completed	Enrollment-495 (18 year or older age group)	2
3	Acalabrutinib Study With Best Supportive Care Versus Best Supportive Care in Subjects Hospitalized With COVID-19.	Acalabrutinib	Completed	Enrollment-177 (18 year -130 year age group)	2
4	A Phase 2 Trial of Infliximab in Coronavirus Disease 2019 (COVID-19)	Infliximab	Completed	Enrollment-17 (18 year or older age group)	2
5	A Study Evaluating the Efficacy and Safety of CKD-314 in Hospitalized Adult Patients Diagnosed With COVID-19 Pneumonia	NafamostatMesilate	Completed	Enrollment-13 (18 year or older age group)	2
6	Convalescent Plasma for the Treatment of COVID-19	Convalescent Plasma	Completed	Enrollment-52 (18 year or older age group)	2

7	Cardiovascular Effects of COVID-19	AT-001	Completed	Enrollment-81 (18 year or older age group)	2
8	Efficacy of Pragmatic Same-day COVID-19 Ring Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland	Lopinavir/ ritonavir	Completed	Enrollment-326 (16 year or older age group)	3
9	VentaProst in Subjects With COVID-19 Requiring Mechanical Ventilation (VPCOVID)	VentaProst	Completed	Enrollment-11 (18 year or older age group)	2
10	Multicenter, Retrospective Study of the Effects of Remdesivir in the Treatment of Severe Covid-19 Infections	Remdesivir	Completed	Enrollment-84 (18 year or older age group)	NA
11	Study of Open Label Losartan in COVID-19	Losartan	Completed	Enrollment-34 (18 year or older age group)	1
12	A Trial of Ciclesonide in Adults With Mild-to-moderate COVID-19	Ciclesonide	Completed	Enrollment-68 (19 year -80 year age group)	2
13	Clazakizumab (Anti-Interleukin 6 (IL-6) Monoclonal) Compared to Placebo for Coronavirus Disease 2019 (COVID-19)	Clazakizumab	Completed	Enrollment-17 (18 year or older age group)	2
14	In Situ Thrombolysis With tPA and Inflow Perfusion Analysis in Patient With Severe Covid-19 Infection	tPA	Completed	Enrollment-15 (18 year -80 year age group)	NA
15	A Multicentre Open-label Two-arm Randomised Superiority Clinical Trial of Azithromycin Versus Usual Care In Ambulatory COVID19 (ATOMIC2) (ATOMIC2)	Azithromycin	Completed	Enrollment-298 (19 year or older age group)	3
16	Stopping ACE-inhibitors in COVID-19 (ACEI-COVID)	ACE inhibitor	Completed	Enrollment-216 (18 year or older age group)	4
17	Pilot Study of CefditorenPivoxil in COVID-19 Patients With Mild to Moderate Pneumonia	Cefditorenpivoxil	Completed	Enrollment-20 (18 year or older age group)	4
18	Hydroxychloroquine in the Prevention of COVID-19 Infection in Healthcare Workers	Hydroxychloroquine	Completed	Enrollment-221 (18 year -75 year age group)	2
19	Cyclosporine in Patients With Moderate COVID-19	Cyclosporine	Completed	Enrollment-11 (18 year or older age group)	1
20	COVID-19 Morbidity in Healthcare Workers and Vitamin D Supplementation	Vitamin D	Completed	Enrollment-128 (18 year -65 year age group)	4
21	Comparison of Two Doses of Enoxaparin for Thromboprophylaxis in Hospitalized COVID-19 Patients (X-Covid 19)	Enoxaparin	Completed	Enrollment-189 (18 year or older age group)	3
22	A Study Evaluating the Efficacy and Safety of CKD-314 (Nafabelltan) in Hospitalized Adult Patients Diagnosed With COVID-19 Pneumonia	NafamostatMesilate	Completed	Enrollment-104 (18 year or older age group)	2
23	Study to Evaluate the Immunogenicity and Safety of Heterologous SARS-CoV-2	Gam-COVID-Vac	Completed	Enrollment-192 (21 year-65 year age group)	2

	Vaccine Schemes				
24	The Effects of Standard Protocol With or Without Colchicine in Covid-19 Infection	Colchicine	Completed	Enrollment-80 (18 year or older age group)	2
25	Efficacy and Safety of Tofacitinib in Patients With COVID-19 Pneumonia (TOFA-COV-2)	Tofacitinib	Completed	Enrollment-414 (18 year or older age group)	2
26	Famotidine in Covid-19 Intensive Care Unit	Famotidine	Completed	Enrollment-60 (18 year-75 year age group)	NA
27	Efficacy of Sofosbuvir Plus Ledipasvir in Egyptian Patients With COVID-19 Compared to Standard Treatment	Sofosbuvir plus Ledipasvir	Completed	Enrollment-250 (18 year-75 year age group)	3
28	The Efficacy of Oral Antiseptics Against SARS-CoV-2	Hypochlorous Acid 0.02% Soln	Completed	Enrollment-75 (18 year or older age group)	4
29	Favipiravir in High-risk COVID-19 Patients	Favipiravir	Completed	Enrollment-500 (50 year or older age group)	3
30	A Real World Study of Bamlanivimab in Participants With Mild-to-Moderate Coronavirus Disease 2019 (COVID-19) (BLAZE-5)	Bamlanivimab	Completed	Enrollment-109 (12 year or older age group)	2
31	Short Term, High Dose Vitamin D Supplementation in Moderate to Severe COVID-19 Disease	cholecalciferol 6 lakh IU	Completed	Enrollment-90 (18 year-80 year older age group)	4
32	An Investigation on the Effects of Icosapent Ethyl (VascepaTM) on Inflammatory Biomarkers in Individuals With COVID-19	Icosapent ethyl	Completed	Enrollment-100 (18 year-75 year age group)	2
33	Heparins for Thromboprophylaxis in COVID-19 Patients: HETHICO Study in Veneto	Low Molecular Weight Heparin	Completed	Enrollment-744 (18 year or older age group)	NA
34	Viral Clearance, PK and Tolerability of Ensovibep in COVID-19 Patients	Ensovibep	Completed	Enrollment-12 (18 year-70 year age group)	2
35	Clinical Trial of the Use of Anakinra in Cytokine Storm Syndrome Secondary to Covid-19	Anakinra	Completed	Enrollment-179 (18 year- 80 year older age group)	2
36	Progesterone for the Treatment of COVID-19 in Hospitalized Men	Progesterone	Completed	Enrollment-40 (18 year or older age group)	1
37	Study of AZD1222 for the Prevention of COVID-19 in Japan	AZD1222	Completed	Enrollment-256 (18 year or older age group)	1,2
38	Prevention With Chloroquine in Health Personnel Exposed to Infection With Coronavirus Disease 2019 (COVID-19)	Chloroquine	Completed	Enrollment-3217 (18 year or older age group)	2
39	First-in-Human Study of Orally Administered GS-441524 for COVID-19	GS-441524	Completed	Enrollment-1 (18 year or older age group)	1
40	Ivermectin for Severe COVID-19 Management	Ivermectin	Completed	Enrollment-66 (18 year or older age group)	3
41	Safety and Efficacy of C21 in Subjects With COVID-19	C21	Completed	Enrollment-206 (18 year- 70 year older age group)	2

42	A Dose Escalation and Dose Expansion Study of NOX66 in the Treatment of COVID-19	NOX66	Completed	Enrollment-41 (18 year or older age group)	1
43	Efficacy and Safety of Ganovo (Danoprevir) Combined With Ritonavir in the Treatment of SARS-CoV-2 Infection	Danoprevir +Ritonavir	Completed	Enrollment-10 (18 year-75 year age group)	4
44	Timing of Corticosteroids in COVID-19	Early-Corticosteroids	Completed	Enrollment-752 (18 year or older age group)	4
45	OD-doxy-PNV-COVID-19 Old Drug " DOXY " for Prevention of New Virus " COVID-19 "	Doxycyclin	Completed	Enrollment-194 (18 year-65 year age group)	3
46	Treatment of SARS Caused by COVID-19 With Ruxolitinib	Ruxolitinib	Completed	Enrollment-77 (18 year or older age group)	1, 2
47	APT™ T3X on the COVID-19 Contamination Rate	Tetracycline hydrochloride 3%	Completed	Enrollment-100 (18 year or older age group)	NA
48	Alpha-1-Antitrypsin-Deficiency in COVID-19	AAT(Alpha 1 Antitrypsin)	Completed	Enrollment-10 (18 year-110 year age group)	NA
49	Effect of Tenofovir/Emtricitabine in Patients Recently Infected With SARS-COV2 (Covid-19) Discharged Home (AR0-CORONA)	tenofovirdisoproxil and emtricitabine	Completed	Enrollment-60 (18 year or older age group)	2, 3
50	TXA127 for the Treatment of Severe COVID-19	TXA127	Completed	Enrollment-22 (18 year or older age group)	2
51	Multi-site Adaptive Trials for COVID-19	SOC + Intravenous Famotidine	Completed	Enrollment-233 (18 year or older age group)	3
52	Study of SOC Plus IVIG Compared to SOC Alone in the Treatment of COVID-19	octagam	Completed	Enrollment-34 (18 year or older age group)	4
53	Clinical-epidemiological Characterization of COVID-19 Disease in Hospitalized Older Adults (COVID-AGE)	Baricitinib or Anakinra	Completed	Enrollment-576 (70 year or older age group)	NA
54	Study of the Outcomes of Olokizumab Therapy in Hospitalized Patients With SARS-CoV-2 (COVID-19) Infection (ROCOVI)	Olokizumab	Completed	Enrollment-1911 (18 year or older age group)	NA
55	The South Proxa-Rescue AndroCoV Trial Against COVID-19	Proxalutamide	Completed	Enrollment-133 (18 year or older age group)	3
56	Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for Hospitalized Adult Patients With COVID-19	REGN10933+REGN combination therapy	Completed	Enrollment-2252 (18 year or older age group)	1, 2
57	Resolving Inflammatory Storm in COVID-19 Patients by Omega-3 Polyunsaturated Fatty Acids -	Omegaven®	Completed	Enrollment-23 (18 year or older age group)	2
58	Clinical Study of Anti-CD147 Humanized Meplazumab for Injection to Treat With 2019-nCoV Pneumonia	Meplazumab	Completed	Enrollment-10 (18 year-75 year age group)	1, 2
59	The Efficacy and Safety of	Pyronaridine-	Completed	Enrollment-113 (19	2

	Pyramax in Mild to Moderate COVID-19 Patients	Artesunate		year or older age group)	
60	Correction of Metabolic Disorders and Its Effect on Respiratory Function of Lungs in Patients With Severe COVID-19 (CARECOVID)	Reamberin	Completed	Enrollment-105 (18 year-70 year age group)	NA
61	Comparison of Viral Particle Dispersion Following Administration of an MDI or Nebulizer in Subjects With COVID-19	albuterol sulfate (MDI)	Completed	Enrollment-14 (18 year or older age group)	NA
62	Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19	Sarilumab	Completed	Enrollment-1912 (18 year or older age group)	2,3
63	Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19)	Dapagliflozin	Completed	Enrollment-1250 (18 year or older age group)	3

Conclusion:

In the past two years, COVID-19 has become an extremely feared pandemic because of the high number of infected people, the rapid spread of the disease, and its severe life-threatening consequences in a significant subset of patients. Globally, this outbreak will have far-reaching socioeconomic effects, such as disruption in education, business, and healthcare. It is clear that effective diagnosis and treatment methodologies based on understanding the microbiology and pathophysiology of this virus are needed. With the information gained from this review, the readers will have a broad understanding of, and be able to interpret, current and future publications and developments in the rapidly evolving field of COVID-19 pandemic.

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