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Review Article

Immunological, Pharmacological, Pharmacokinetics, Therapeutic Targets and Various Therapy for SARS-CoV-2: Recent Advancement and Future Prospective

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Abstract

Severe acute respiratory syndrome 2 (SARS-CoV- 2) is a novel coronavirus that causes coronavirus disease 2019 (COVID-19), an infection characterized by flu-like symptoms, progressing in some cases to acute respiratory distress syndrome (ARDS). That WHO to declare it as global pandemic. Based on the information gained from the responses to other RNA coronaviruses, including the strains that cause severe acute respiratory syndrome (SARS)-coronaviruses and Middle East respiratory syndrome (MERS), effort are put in place to develop effective therapeutic agent against the COVID-19. Currently, there is no therapeutic candidate for this virus but the United States Food and Drug Administration (FDA) has provided emergency authorization for the use of chloroquine and hydroxychloroquine and other promising antiviral drugs. Although the result of ongoing clinical trials are not out, but some provide promising result *in vitro*. The most important factor associated with pathophysiology of SARS-CoV-2 is the host immune response which results due to binding of spike glycoprotein to its receptor angiotensin-converting enzyme 2 (ACE2) but concerned has arose for the continuous expressing of ACE in affected patient especially patient with pregnancy as this might increase the susceptibility of the patient although there is no strong evidence for it involvement for susceptibility of the affected patients. Despite the continuous evolving and dynamics on the literature of COVID-19, using the existing knowledge, possible drug target have been identified for the development of the effective vaccine. Since there is no effective therapeutic drug for the current pandemic, drug repurposing might be a viable strategy and specific prophylaxis regimen should be provide to reduce the toxicity on the affected patients and the clinical trial should be based on the specificity and efficacy of the drug. This review provide information on the Novel invention and new guidelines or protocol for SARS-COV-2.

Keywords: Immunological; Pharmacological; Theraputics Targets; Recent Advancements; SARS-CoV-2

Introduction

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is a novel coronavirus that causes coronavirus disease 2019 (COVID-19), an infection characterized by flu-like symptoms, progressing in some cases to acute respiratory distress syndrome (ARDS). This novel *Betacoronavirus* is similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV); based on its genetic proximity, it likely originated from bat-derived coronaviruses with spread via an unknown intermediate mammal host to humans. The outbreak has since rapidly spread to other provinces in mainland China, as well as other countries around the world, and as of June 28, 2020, more than ten million cases has been reported with more than 490,000 fatality (https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases). The coronavirus COVID-19 is affecting 213 countries and territories around the world and 2 international conveyances. The outbreak has created a global health crisis that led to the chaos and a deep impact on the way we perceive our world and our everyday lives. Not only the rate of contagion and patterns of transmission threatens our sense of agency, but the safety measures put in place to contain the spread

of the virus also require social distancing by refraining from doing what is inherently human, which is to find solace in the company of others [1].

Currently, more than a billion Indians stand at the rock face of massive increase in cases of corona virus disease (COVID-19) pneumonia. There are no proven effective drugs for the treatment of SARS-COV 2 virus infection, although some have been tried. In this session we will review and highlight specific drug of choice approved by the Indian government for the management and treatment of COVID-19 pneumonia.

The most important factor associated with pathophysiology of SARS-CoV-2 is the Host immune response which results due to binding of spike glycoprotein to its receptor angiotensin-converting enzyme 2 (ACE2). The increased morbidity and mortality rate in COVID-19 is largely associated with acute respiratory distress syndrome (ARDS) therefore; it's considered as an principle clinical condition which results to tremendous consequence in SARS CoV-2. ARDS is most common in clinical complications such as pneumonia, sepsis, pancreatitis, and blood transfusion. ARDS is characterised by the increased lung permeability and the exudation of protein-rich pulmonary edema fluid into the airspaces, which ultimately results to respiratory insufficiency and damage in the blood-air barrier (alveolar–capillary membrane) [2].

Currently, no drugs or therapeutics vaccines have been approved by the FDA for the treatment of covid-19 pneumonia. Given rapid and catastrophic spread of COVID-19, there is an urgent need to explore pre-existing therapeutic options while novel therapies and vaccines are being developed. Some pharmacological treatment has gained utmost popularity in emergency use authorization from FDA based on preliminary data displaying a faster time to recovery of hospitalized patients with severe covid-19 infection. However, there are several clinical trials on potential antiviral therapies taking place in order to examine their efficacy and safety in management and the treatment of the novel corona virus. Some of these clinical trials have yielded promising results while some are still ongoing.

Since drug development is a challenging task and requires a long period of time, it cannot meet the urgent needs of the moment. Therefore, using the existing drugs to cut off the above process of the virus is expected to make a breakthrough in a short time, on the premise of understanding the invasion, replication, and release mode of the virus. There is a special group in this outbreak, pregnant women, which deserve our great attention because of the physiological changes during pregnancy that make them more susceptible to virus. Previous epidemiological evidence strongly suggests that pregnant women have a higher risk of serious illness and death from viral infections. The number and efficacy of drugs that can be used to treat pregnant women who are afflicted with other diseases are extremely limited.Based on the available online data and published work on COVID-19, we review the novel invention and new guidelines or protocols on SARS-COV-2.

Background

Using available online resources, we've reviewed numerous articles published online with a view of searching and finding recent updated on the current pandemic of SARS-COV-2, the virus that cause novel Coronavirus 2019 (COVID-19) including all the available therapeutics, notable drug target of the virus, the ongoing clinical trial for the development of effective therapeutic candidate of the virus and other related family, viral replication and mechanism of action of the repurposed drugs used in the treatment, development of therapy, toxicity of the drugs used, suspected drug targets. Consideration was also made on the available data for the effect of covid-19 on pregnancy and management of pregnant woman affected with COVID-19. Due to dynamics nature and continuous evolving of literature regarding the treatment of SARS-COV-2, the data search also elaborated on the immune response and potential of immunomodulatory agents used for treatment of COVID-19, pharmacokinetics and pharmacodynamics of the COVID-19, doses and compensation of the drugs, toxicity, contraindications of the drugs, additional drug target and targeting potential entry mechanism of COVID-19, the role of angiotensin converting enzymes inhibitors (ACEi) on SARS-COV-2, recent updates on covid-19, and limitations. Keywords like 'COVID-19', 'cytokines', 'coronavirus' and 'immunotherapy', 'ACEi', 'severe acute respiratory syndrome coronavirus 2, 2019-nCoV, SARS-CoV-2, SARS-CoV, MERSCoV, and COVID-19 in combination with treatment and pharmacology. 'Clinical trial for covid-19' were used to search for key articles from Google Scholar, MEDLINE, NCBI, UpToDate, and Web of Science. We included scientific publications from February 2014 to June, 2020. Articles focusing on clinical features, immune response, and immunomodulatory agents treatment of COVID-19 were eligible for inclusion.

Treatment modalities of covid-19, earlier, present and recent advances

Immune response against SARS CoV-2

The most important factor associated with pathophysiology of SARS-CoV-2 is the Host immune response which results due to

binding of spike glycoprotein to its receptor angiotensin-converting enzyme 2 (ACE2). Cryogenic electron microscopy and surface Plasmon resonance shows the similarities and minor differences between SARS-CoV-2 and SARS S proteins. However, the affinity of SARS-CoV-2 S protein binding to ACE2 is 10 to 20 times higher than that of the SARS S protein; as such SARS COV-2 is transmitted rapidly among humans than SARS COV.The increased morbidity and mortality rate in COVID-19 is largely associated with acute respiratory distress syndrome (ARDS) therefore; it's considered an important clinical condition which results to tremendous consequence in SARS CoV-2 [3]. ARDS is most common in clinical complications such as pneumonia, sepsis, pancreatitis, and blood transfusion. ARDS is characterised by the increased lung permeability and the exudation of protein-rich pulmonary edema fluid into the airspaces, which ultimately results in to respiratory insufficiency and damage in the blood-air barrier (alveolar–capillary membrane). Elevated level of pro-inflammatory cytokines (eg, Interferon γ, interleukin (IL-) 1B, IL-6, IL-12) and chemokines (CXCL10, CCL2) is one of the classical feature seen in both SARS, and MERS infections, however, in SARS CoV-2 it was reported that patients requiring ICU admission displayed higher concentrations of CXCL10, CCL2 and TNFα as compared to those in which the infection was less severe and did not require an ICU admission [3].

Immunomodulatory agents

Interleukin-1 receptor antagonist (IL-1RA) is a humanized protein encoded by *IL1RN* gene which bind specifically to the cell surface of interleukin-1 receptor (IL-1R), the same receptor that binds interleukin 1 (IL-1), thereby preventing IL-1 signalling.

Anakinra (ANK) is a non-glycosylated, recombinant form of human IL-1 receptor approved by the FDA in 2001, which mainly inhibit binding to the IL-1 receptor and prevent activation of this receptor by either IL-1β or IL-1α Potential role of ANK in the treatment of respiratory dysfunction in COVID-19 patients has been reported, with need to further investigate the clinical efficacy and safety of this immunomodulatory agent.

In a multi-centre study which examine the clinical efficacy of ANK in 41 patients with refractory Adult-onset still's diseases (AOSD), it was realised that ANK yielded rapid and maintained clinical and laboratory improvement in these patients. However, despite the limitations of the study, randomized clinical trials are required to critically elaborate on the effectiveness of IL-1 receptor blockade in AOSD and other disease including COVID-19.

Interleukin-6 receptor antagonist (IL-6RA): Are mainly used for the treatment of Rheumatoid Arthritis, Systemic Juvenile Idiopathic Arthritis, Cytokine Release Syndrome, and Giant Cell Arthritis [4].

Tocilizumab also known as atlizumab, is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). Interleukin 6 (IL-6) is a cytokine that plays an important role in immune response; the immunosuppressive drug is widely used for the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis and other autoimmune diseases.

Efficacy and safety of tocilizumab (IL-6RA) was confirmed in 21 patients diagnosed with severe COVID-19 Patients. The temperature of all the patients returned to normal, respiratory function improved significantly, 20 patients have been recovered and discharged within 2 weeks after the tocilizumab therapy, 1 patient is recovering. Interestingly, no adverse drug reactions were reported during the treatment with tocilizumab. However, a multicentre, large-scale clinical trial (ChiCTR2000029765) has been launched to further confirm the effectiveness of the treatment.

Another study which examined the effectiveness of treatment with tocilizumab shows improvement in patients diagnosed with severe COVID-19 where Fever returned to normal on the first day, and other symptoms improved remarkably within a few days. Within 5days after tocilizumab, 15 of the 20 patients had lowered their oxygen intake, and 1 patient needed no oxygen therapy with normal CT scans, decreased percentage lymphocytes in peripheral blood and significant decreased in C reactive protein level [5].

TNF-α blockers (Tumor necrosis factor alpha) are type of drugs that suppress immune system by blocking the activity of TNF-α (an important pro-inflammatory cytokine mostly expressed by immune cells and other cells that promote inflammation). Uncontrolled secretion of TNF-α has a pathogenic role in some inflammatory conditions such as Rheumatoid arthritis, psoriatic arthritis, crohn's disease, and ankylosing spondylitis.

Studies in animal models shows that neutralizing the activity of TNFs or blocking their receptors yield a protective strategy and decreases morbidity and mortality rate of induced SARS-CoV.

A research article shows recovery with regression of fever, cough and myalgia at day 10 along with a decreased CRP level by a subcutaneous administration of TNF-α inhibitor such as etaner-

cept 50 mg and methotrexate 20 mg to 60 years old COVID-19 individual suffering from spondyloarthritis [6].

Corticosteroids are synthetic drugs which imitate cortisol (steroid hormone produced by adrenal gland) and most commonly used for treatment of autoimmune diseases, asthma and skin conditions. They tackle with wide range of processes in the body, such as regulation of blood pressure, suppressing inflammatory activities, metabolism, and bone formation.

A Systematic review and meta-analysis examining the efficacy and safety of corticosteroids in COVID-19 patients with ARDs shows a promising result, while the results are inconsistence in patients without ARDs.

On contrary, another systematic review and meta-analysis shows that severe COVID-19 patients more likely require corticosteroids for suppressing immune response, while those with mild and moderate conditions are not recommended for treatment with corticosteroids because corticosteroids could lead to high mortality, longer length of stay, high rate of bacterial infection and hypokalaemia. However, more multicentre clinical trials are needed to further verify this conclusion.

Advances in therapeutic development

Remdesivir

Remdesivir (Development code GS-5734) is a broad-spectrum antiviral drug. The drug has not been licensed or approved at the time of writing this article. Gilead sciences in 2017 during Ebola outbreak, synthesized Remdesivir, a mono phosphoramidite prodrug, and an analog of ATP.

Inactive Remdesivir is converted into its active form (GS-441524) which primarily act to inhibit transcription of the viral DNA by competing with ATP for incorporation into RNA to deplete the energy and nucleotide source thereby inhibiting viral RNA-dependent RNA polymerase action. This ultimately leads to a decrease in the viral replication and termination of the RNA transcription. Remdesivir showed appreciable antiviral activity against many variants of the Ebola virus in cell-based assays, However, the drug is under trial for its potential use in the treatment of SARS-CoV2, that is responsible for COVID-19.

Similarly, i*n-vitro* studies showed that remdesivir can inhibit replication of some variants of coronaviruses like SARS-CoV and MERS-CoV. In an *in-vitro* test using epithelial cell cultures of a primary human airway, remdesivir was effective against Bat-CoVs, and circulating contemporary human-CoV in primary human lung cells.

A research article shows that remdesivir might be considered as a treatment option for COVID-19 patients. Due to the high perception of scientists on the use of remdesivir as a potential therapeutic target, a randomized, controlled, double-blind clinical trial is planned to evaluate the safety and effectiveness of remdesivir in adults with mild or moderate COVID-19 respiratory disease.

Furthermore, a randomized, double-blind, placebo-controlled, multicentre study already in phase 3 is evaluating the efficacy and safety of remdesivir in 452 hospitalized adult patients with severe COVID-19. However, Clinical trials associated with efficacy remdesivir in COVID-19 patients are currently underway, both in China and the USA at the same time the drugs should be avoided in the presence of underlining health conditions [7].

Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are potent derivatives of quinoline molecule which are used as antimalarial drugs while hydroxychloroquine is frequently used as an antirheumatic agent. Both drugs have similar clinical indications and side effects despite their varying therapeutic dosage which include retinal toxicity commonly referred to as chloroquine retinopathy or 4AQ retinopathy.

Due to absence of an effective treatment against COVID-19 and an alarming exponential increase in the number of infections as shown in figure 3, Chloroquine and its analog Hydroxychloroquine are largely being used for the treatment of the disease. Although preventive measures were imposed worldwide to reduce the spread of the pandemic, clinicians have to redirect some of the FDA approved antiviral drugs to other medical conditions for the treatment of COVID-19, although the safety and benefit of these treatment regimens remain ambiguous.

A multi-national registry analysis of 96,032 patients requiring hospitalization (average age 53·8 years, 46·3% women) with COVID-19 shows that use of Chloroquine or hydroxychloroquine (with or without a macrolide) has no therapeutic benefit, It is rather associated with an increased risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19. However, the

findings logically suggest that these drug regimens should not be used outside of clinical trials and urgent confirmation from randomized clinical trials is needed. Regrettably, three of the authors (Mandeep R. Mehra, MD, MSc, Frank Ruschitzka, MD, Amit N. Patel, MD) of the paper have retracted their study on 4th June, 2020 as they are unable to complete an independent audit of the data underpinning their analysis. As a result, they have concluded that they "can no longer vouch for the veracity of the primary data sources [8].

A recent study published at medRxiv has partially confirmed the potential of hydroxychloroquine in the treatment of COVID-19 under reasonable management, looking at the fact that no better option for treatment of the virus is confirmed at present. However, there is need for Large-scale clinical researches to shed more

Glecaprevir and maraviroc

Glecaprevir: Is a direct antiviral agent and Hepatitis C virus protease inhibitor that inhibits the viral RNA replication. Glecaprevir/pibrentasvir combination is therapeutically useful for patients who experienced therapeutic failure from other NS3/4A protease inhibitors. It showed a high genetic block against resistance mutations of the virus. Maraviroc is an antagonist drug of chemokine receptor designed to act against HIV by interfering with the interaction between HIV and CCR5 and was approved for use by the FDA in August 2007.

A recent article published shows the binding of FDA approved drugs; Glecaprevir and Maraviroc to the substrate-binding pocket of SARS-CoV-2 main protease Inhibit SARS-CoV-2 main protease. Therefore, a combination of these approved drugs can be considered as another therapeutic target for COVID-19. However, experimental validation and clinical manifestation are required to strongly support the findings [9].

Respiratory therapy

Oxygen therapy is mostly applicable in mild and moderate stages of the disease. Early recognition and immediate referral of patients with worsening respiratory functions such as hypoxemia, respiratory distress, or shock with target SpO2 > 94% on conventional oxygen therapies, such as face masks with reservoir bags are important as a respiratory supportive measure as per the WHO guidelines. In patients with COVID-19, there is a potential for a worsening of hypoxia and an increased need for intubation and invasive mechanical ventilation under close monitoring, if sufficient high arterial O_2 level ($SatO_2$ 93–96%) is not reached, and if acute lung injury develops (ratio of the arterial partial pressure of oxygen to fractional inspired oxygen ≤ 200 mmHg).

Specific drugs of choice in India for the treatment of covid-19

Currently, more than a billion Indians stand at the rock face of massive increase in cases of corona virus disease (covid-19) pneumoni. Yet t here are no established and effective drugs for the treatment of SARS-COV 2 virus infection, although some have been tried. In this session we will review and highlight specific drug of choice approved by the Indian government for the management and treatment of COVID-19 pneumonia [11].

Hydroxychloroquine prophylaxis

The anti-viral and anti-inflammatory actions of chloroquine have led to numerous trials urgently in the face of global health emergency. A Chinese study involving more than 100 patients of COVID-19 found chloroquine superior to the control group in reducing symptom duration, exacerbation of pneumonia including radiological improvement and promoting virus-negative seroconversion without any severe side effects. Studies have shown that chloroquine is a proven anti-malarial drug that has the capability of inhibiting the replication of several intracellular micro-organisms including coronaviruses.

The Indian Council of Medical Research, under the ministry of health and family welfare, has recommended chemoprophylaxis with hydroxychloroquine (400 mg twice on day 1, then 400 mg once a week thereafter) for asymptomatic health care workers treating patients with suspected or confirmed covid-19, and for asymptomatic household contact of confirmed cases. The use of hydroxychloroquine in prophylaxis is derived from available evidence of benefits as treatment and supported by preclinical data. Although some in vitro evidence supports the antiviral activity of hydroxychloroquine and its precursor chloroquine.

Methylprednisolone

According to Clinical Management Protocols of covid-19 issued by the Indian Government under the ministry of health and family welfare recommended the use of methylprednisolone 0.5 to 1 mg/kg for 3 days (preferably within 48 hours of admission or if oxygen requirement is increasing and if inflammatory markers are increased) in moderate cases of covid-19.

Remdesivir

Remdesivir (GS-5734) is by far the most promising drug that exhibits broad-spectrum antiviral activities against RNA viruses basically. It is a prodrug, whose structure resembles adenosine. Therefore, it can incorporate into nascent viral RNA, and further inhibit the RNA-dependent RNA polymerase. Indian Ministry of health and family welfare recommended Remdesivir to be used in treatment of covid-19 infection in patients with moderate disease (those on oxygen) with none of the following contraindications:

- AST/ALT > 5 times Upper limit of normal (ULN)
- Severe renal impairment (i.e., eGFR < 30ml/min/m2 or need for hemodialysis)
- Pregnancy or lactating females
- Children (< 12 years of age)
- Dose: 200 mg IV on day 1 followed by 100 mg IV daily for 5 days

Tocilizumab

Also Tocilizumab has been recommended to be used in patients with moderate disease with progressively increasing oxygen requirements and in mechanically ventilated patients not improving despite use of steroids. Special considerations before its use include:

- Presence of raised inflammatory markers (e.g., CRP, Ferritin, IL-6)
- Patients should be carefully monitored post Tocilizumab for secondary infections and neutropenia
- Active infections and Tuberculosis should be ruled out before use.
- Dose: 8mg/kg (maximum 800 mg at one time) given slowly in 100 ml NS over 1 hour; dose can be repeated once after 12 to 24 hours if needed.

Favipiravir

Favipiravir is approved in Japan in 2014 for the treatment of novel or re-emerging influenza virus infections. It has a unique mechanism of action: it is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and recognized as a substrate by viral RNA polymerase, thereby inhibiting RNA polymerase activity (Glenmark Becomes the First Pharmaceutical Company in India to Receive Regulatory Approval for Oral Antiviral Favipiravir, for the Treatment of Mild to Moderate COVID-19, n.d.). In a landmark development for COVID-19 patients in India, Glenmark Pharmaceuticals, a research-led, integrated global pharmaceutical company, has announced the launch of antiviral drug Favipiravir for the treatment of mild to moderate COVID-19 infection.

Drug targets for SARS-COV-2

Spike (S) protein

The spike protein is a clove-shaped, type I-TM protein. The spike protein has three segments that are ectodomain (ED) region, TM region, and intracellular domain, which comprises the intracellular short tail part [12]. The receptor-binding S1 domain (three S1 heads) and the membrane fusion subunit S2 (trimeric stalk) on C-terminal together comprise the ED. Spike proteins gather in the trimeric form on the outer surface of the virion, giving it the appearance of a crown, due to which it is called CoV. The spike protein plays an important role in virus entry into the host. Initial interactions between the S1 domain and its host receptor (ACE2 in case of SARS-CoV and PP 4 In case of MERS-CoV) and subsequent S2 segment mediated fusion of the host and viral membranes allow the CoV- RNA genome to enter inside the host cells and thus, these proteins represent as important targets from drug discovery side. The spike protein also activates the immune response of the host cell toward CoV [12].

Drug designing strategies targeting S protein and its interaction

The RBD is targeted in many drug designing studies. A peptide sequence with sequence similarity to the RBD of S protein hampered S1-RBD: ACE-2 interaction and prevented entry of SARS-CoV into Vero cells (IC_{50} around 40 μM).Chloroquine, an antimalarial agent, inhibits SERS-CoV by elevation of endosomal pH and alters the terminal glycosylation of ACE-2, which ultimately interferes with the virus receptor binding.Monoclonal antibody can be generated by immunizing the spike protein of SERS-CoV (transgenic mice) or from the B-cells of CoV-infected persons. Spike-specific monoclonal antibodies 80R and CR301 block the S-ACE-2 interactions and thus neutralize infection by human SARS-CoV (HKu39849 and Tor2) and palm civet strain (SZ3) [14].

E protein

The E protein is the smallest (8.4–12 kDa size) TM structural protein of CoV. Two distinct domains comprise the E protein: the hydrophobic domain and the charged cytoplasmic tail. However, the structure is highly variable among different members of the

CoV family. The E protein has a special role in viral morphogenesis, especially during assembly and egress. CoVs lacking E protein show lower viral titer, immature, and inefficient progenies. It plays an important role in virus assembly, membrane permeability of the host cell and virus host cell interaction. Apart from this, E protein found around the ER and Golgi body regions (Figure 1). Hexamethylene amiloride blocks this E protein-associated ion channel activity in the mammalian cells expressing SERS-CoV envelop protein.

M protein

The M protein interact with envelop protein in the budding compartment of the host cell. The interaction between the virus and the host may be related to the glycosylation of the M protein and therefore, M protein believed to be central organizer of coronavirus assembly and determine the shape of viral envelop The M protein is characterized by three TM domains with C-terminal inside (long) and N-terminal (short) outside [15].

The M protein and the N protein are the major viral envelope proteins, defining viral shape, but it also takes part in the formation and release of virus-like particles.

Through protein–protein interactions, the M protein plays a crucial role in viral intracellular homeostasis (Schoeman D, and Fielding B, 2019). Interaction between M–M, M–S, and M–N proteins takes a special part in viral assembly. The M–S interactions are necessary for the interaction of spike protein in the ERGIC complex, also known as the Golgi complex, which is later incorporated into new viral progenies. The M–N interactions are crucial for the stabilization of the RNP complex (nucleocapsid–RNA complex), which forms the viral core [15].

Nucleocapsid proteins (N)

The structure of nucleocapsid protein (N protein) is conserved across different members of the COV family. The three characteristic intrinsically disordered regions (IDRs) of the nucleocapsid (N) protein are the N-arm, central linker (CL), and the C-tail. The NTD and the CTD are the major structural and functional domain of the nucleocapsid protein. The most important function of the N protein NTD is RNA binding, while the primary job of the CTD is dimerization. As the CL region is rich in arginine and serine residue content, it also contains a large number of phosphorylation sites. The C-terminal IDRs take an important part in nucleocapsid protein oligomerization and N–M protein interactions [16].

Proteases

The SERS-CoV genome encodes a number of proteins. The replicase gene, which is a major component of the CoV genome encoded for 16 NSPs in the form of two large PPs (PP1a and PP1ab). Two types of cysteine proteases act on these PPs to release the NSPs. The C-terminal end of these PPs is cleaved by chymotrypsin-like cysteine protease (main protease [M^{pro}] or 3C-like protease [3CL-pro]) and the N-terminal end is processed by the M^{pro} (also known as papain-like protease [PL^{pro}]). The first three cleavage sites of the PPs is cut by PL^{pro} while the rest 11 sites are cleaved by CL^{pro}, and this cleavage results in release of 16 NSPs [16].

Papin-like protease PL^{pro}

A viral protease responsible for the cleavage of viral peptides in to functional protein for virus replication and packaging within the host. The N-terminal of these PPs is processed by the papain like protease PL^{pro}. The PL^{pro} cleaves the N-termial region of the PPs to generate three non –structural proteins,NSPs (NSP1, NSP2 and NSP3). High dose of Zinc and Zn conjugate were found to inhibit boyh types of SARS protease (CL^{pro} and PL^{pro}).

Chymotrypsin-like Cysteine Protease $3CL^{pro}$

A viral protease responsible for the cleavage of viral peptides in to functional protein for virus replication and packaging within the host. Two type of cysteine protease act on these PPs encoded from the Cov-genome to release 16NSPs. The C-terminal end of these PP is cleaved by chymotrypsin like cysteine protease (Main protease [Mpro] or $3CL^{pro}$). The 3CLpro is present in homodimer form and has Cys-His dyad on active site which shows protease activity [27]. If mutated on the Ser139 and phe140 positions, it abolishes the dimerization of 3CLPro (PDB ID: 3F9G). This protease can cleave 11 sites in the p1 position of PP1a and PP1ab and can produce a mature protein that anchors the replication/transcription complex and also releases the mature NSPs.

Hemagglutinin esterases HE

This HE enzyme is present in the envelope of CoV, more specifically among beta coronaviridiae. The HE is a marker of CoV and influenza virus evolution. HE mediates reversible attachment to O-acetylated-sialic-acids by acting both as lectins and as receptor-destroying enzymes. Interactions between HE in complex with sialic acid can be visualized in PDB ID: 3CL5.

NTPase/Helicases

NTPase/helicase plays a vital role in the central dogma of the virus (Frick D, and Lam A., 2006). SARS-CoV helicase enzyme is a member of the SF1. This enzyme prefers ATP, dATP, and dCTP as substrates; it also hydrolyzed all NTPs. Toxicity issues are main obstacles in the development of inhibitors of helicase, and nonspecificity of inhibitors may cause serious toxicity. However, despite theoretical limitations, helicase is being increasingly recognized as a druggable target for different disease conditions.

Notable clinical trials for sars-cov 2

Currently, there is no sufficient evidence that any existing antiviral drugs can efficiently treat COVID-19 infection. However, there are several clinical trials on potential antiviral therapies taking place to examine their efficacy and safety in management and the treatment of the novel corona virus. Some of these clinical trials have yielded promising results while some are still ongoing. Therapies can be divided into two categories depending on their target. One is acting on the coronavirus directly, either by inhibiting crucial viral enzyme responsible for genome replication, or by blocking viral entry to human cells. The other is designed to modulate the human immune system, either by boosting the innate response, which has a particularly important role against viruses, or by inhibiting the inflammatory processes that cause lung injury [17] table 1. Review and highlight different notable clinical trials for SARS-COV 2.

S/N	Intervention	Title of the study	Location of the study	Status	Beginning/estimated end	Phase	References
1	Duvelisib	A Pilot Study of Duvelisib to Combat COVID-19	USA	Not yet recruiting	June 30, 2020 to December 31, 2021	Phase 2	[51]
2	Tranexamic acid and Placebo oral tablet	Exploratory Studies of the Effect of Tranexamic Acid Treatment on the Progression of COVID-19 in patients.	USA	Not yet recruiting	September 30, 2020 to December 31, 2020.	Phase 2	[52]
3	Estradiol patch	Phase II clinical trials of Estradiol to reduce severity of COVID-19 infection	USA	Recruiting	April 20, 2020 to November 15, 2020	Phase 2	[53]
4	Clazakizumab	A phase ii trial to evaluate the safety and tolerability of clazakizumab compared to placebo for the treatment of covid-19 infection	USA	Recruiting	April 24, 2020 to March 31, 2021	Phase 2	[54]
5	Mavrilimumab	A phase 2/3, randomized, double blind, placebo controlled study to evaluate the efficacy and safety of mavrilimumab (KPL-301) treatment in adults subjects hospitalized with severe covid-19 pneumonia and hyperinflammation	USA	Not yet recruiting	June 2020 to April 2021	Phase 2	[55]
6	Oxyhydrogen	Hydrogen-Oxygen generator with Nebulizer in the improvement of symptoms in patients infected with covid-19	China	Recruiting	February 15, 2020 to August 01, 2020	Not applicable	[56]
7	Bevacizumab	Bevacizumab in severe or critically severe patients with covid-19 pneumonia-RCT	China	Recruiting	March 17, 2020 to July 31, 2020	Not applicable	[57]

8	Sildenafil citrate tablets	A Pilot Study of Sildenafil in covid-19	China	Recruiting	February 09, 2020 to November 09, 2020	Phase 3	[58]
9	Moxibustion plus Cupping	Moxibustion plus Cupping in convalescent patients with covid-19. A Randomized clinical trial.	China	Recruiting	May 10, 2020 to December 2021	Not applicable	[59]
10	Fingolimod 0.5 mg	Fingolimod in covid-19	China	Recruiting	February 22, 2020 to July 01, 2020	Phase 2	[60]
11	Abidol hydrochloride, Oseltamivir, Lopinavir/ritonavir	A Prospective/Retrospective Randomized controlled clinical study of antiviral therapy in 2019 n COV pneumonia	China	Not yet recruiting	February 01, 2020 to July 01 2020	Phase 4	[61]
12	Abidol hydrochloride and Abidol hydrochloride combined with interferon atomization	A Prospective/Retrospective Randomized controlled clinical study interferon atomization in 2019 n COV pneumonia	China	Not yet recruiting	February 01, 2020 to July 01 2020	Phase 4	[62]
13	Darunavir and Cobicistat	Efficacy and safety of Darunavir and Cobicistat for treatment of covid-19	China	Recruiting	January 30, 2020 to December 31, 2020	Phase 4	[63]
14	Enoxaparin	Comparison of Two doses of Enoxaparin for thromboprophylaxis in Hospitalized covid-19 patients	China	Recruiting	May 14, 2020 to November 2020	Phase 3	[64]
15	Radiation: Single fraction whole lung radiotherapy	Pilot Study on the Feasibility of Low Dose Radiotherapy for SARS-Cov-2 **Pneumonitis** **(**COVID-19 Low Dose Radiotherapy - COLOR 19)	Italy	Recruiting	May 10, 2020 to July 23, 2022	Not applicable	[65]
16	Tocilizumab	Efficacy and Safety of Tocilizumab in the Treatment of Patients With Respiratory Distress Syndrome and Cytokine Release Syndrome Secondary to COVID-19: a Proof of Concept Study	Italy	Recruiting	April 01, 2020 to March 31, 2021	Not applicable	[66]
17	Escin and standard therapy	Efficacy and Safety of Escin as add-on Treatment in Covid-19 Infected Patients	Italy	Recruiting	March 23, 2020 to August 30, 2020	Escin: phase 2 Standard therapy; phase 3	[67]
18	Emapalumab and Anakinra	Efficacy and safety of Emapalumab and Anakinra in reducing hyperinflammation and respiratory Distress in patient with covid-19 infection	Italy	Recruiting	April 2, 2020 to September 2020	Emapalumab; phase 2 Anakinra: phase 3	[68]

19	Cytokine Adsorption	Pilot Study on Cytokine Filtration in COVID-19 ARDS (Cytok-COVID19)	Italy	Recruiting	April 17, 2020 to July 2020	Not applicable	[69]
20	Bemiparin	A Randomized, Single-blind Study With a Parallel Control Group on the Efficacy and Safety of Bemiparin at Therapeutic Dose vs. Prophylactic Dose in Patients Hospitalized for COVID-19	Spain	Recruiting	June 4, 2020 to March 31, 2021	Phase 2	[70]
21	Ivermectin and placebo	Pilot Study to Evaluate the Potential of Ivermectin to Reduce COVID-19 Transmission	Spain	Recruiting	May 14, 2020 to August 30, 2020	Phase 2	[71]
22	ACE inhibitor and ARB	Evaluation of Influenza Vaccination and Treatment With ACEI and RAIII in the Evolution of SARS-Covid19 Infection	Spain	Recruiting	March 01, 2020 to August 31, 2020	Phase 1	[72]
23	Galidesivir and placebo	A Phase 1b Double-blind, Placebo-controlled, Dose-ranging Study to Evaluate the Safety, Pharmacokinetics, and Anti-viral Effects of Galidesivir Administered Via Intravenous Infusion to Subjects With Yellow Fever or COVID-19	Brazil	Recruiting	April 9, 2020 to May 31, 2021	Phase 1	[73]

Table 1: Notable Clinical trials of SARS-COV-2.

Dose compensation of antiretroviral and other important drugs

Antiretroviral drugs inhibit the reproduction of retroviruses—viruses composed of RNA rather than DNA. The best known of this group is HIV, human immunodeficiency virus, the causative agent of AIDS. Antiretroviral agents are virustatic agents which block steps in the replication of the virus. The drugs are not curative; however continued use of drugs, particularly in multi-drug regimens, significantly slows disease progression.

There are three main types of antiretroviral drugs, although only two steps in the viral replication process are blocked. Nucleoside analogs, or nucleoside reverse transcriptase inhibitors (NRTIs), such as didanosine (ddI, Videx), lamivudine (3TC, Epivir), stavudine (d4T, Zerit), zalcitabine (ddC, Hivid), and zidovudine (AZT, Retrovir), act by inhibiting the enzyme reverse transcriptase. Because a retrovirus is composed of RNA, the virus must make a DNA strand in order to replicate itself. Reverse transcriptase is an enzyme that is essential to making the DNA copy. The nucleoside reverse transcriptase inhibitors are incorporated into the DNA strand. This is a faulty DNA molecule that is incapable of reproducing.

Doses recommendation ARV must be individualized based on the patient and use of interacting drugs. The optimum combinations of antiretroviral drugs have not been determined, nor is there agreement on the stage of infection at which to start treatment. In fact, starting treatment too early has led to unwanted side effects in some patients or problems with patient readiness to comply. Treatment should begin when the time and circumstances are right. Table 2A review different ARV drugs and the dosage used in different individuals, table 2B review the infant prophylaxis for ARV dosing [18].

Toxicity of drugs for COVID-19

Drug toxicity refers to how poisonous a drug can be. It describes any undesirable effect of a drug that occur beyond its anticipated therapeutic effects in clinical use. In the context of pharmacology, drug toxicity occurs when a person has accumulated too much of a drug in his bloodstream, leading to adverse effects on the body. Drug toxicity may occur when the dose is given is too high or the liver or kidneys are unable to remove the drug from the bloodstream, allowing it to accumulate in the body [19].

Generic name	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine (AZT)	250–300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	400–600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily
Proteases inhibitors (PIs)	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg once daily
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg once daily[a] or 600 mg + 100 mg twice daily[b]
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily
	Considerations for individuals receiving TB therapy In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin, adjusted dose of LPV/r: (LPV 800 mg + RTV 200 mg twice daily or LPV 400 mg + RTV 400 mg twice daily).or, SQV/r (SQV 400 mg + RTV 400 mg twice daily), with close monitoring.
Integrase strand transfer inhibitors (INSTIs)	
Dolutegravir (DTG)	50 mg once daily
Raltegravir (RAL)	400 mg twice daily

Table 2A: Dosage of antiretroviral drugs for adults and adolescents.

Source: (Ministry of Health and Family welare of India, 2013).

a. For individuals with no previous use of protease inhibitors.

b. For individuals with previous use of protease inhibitors.

Infant age	Dosing of NVP	Dosing of AZT
Birth to 6 weeks		
Birth weight 2000–2499 g	10 mg once daily (1 ml of syrup once daily)	10 mg twice daily (1 ml of syrup twice daily)
Birth weight ≥2500 g	15 mg once daily (1.5 ml of syrup once daily)	15 mg twice daily (1.5 ml of syrup twice daily)
>6 weeks to 12 weeks		
	20 mg once daily (2 ml of syrup once daily or half a 50 mg tablet once daily)	No dose established for prophylaxis; use treatment dose 60 mg twice daily 6 ml of syrup twice daily or a 60 mg tablet twice daily)

Table 2B: Simplified infant prophylaxis dosing for ARV.

Source: (Ministry of Health and Family welare of India, 2013).

a. For infants weighing <2000 g and older than 35 weeks of gestational age, the suggested doses are: NVP 2 mg/kg per dose once daily and AZT 4 mg/kg per dose twice daily. Premature infants younger than 35 weeks of gestational age should be dosed using expert guidance.

Occurrence

Drug toxicity can occur as a result of the over-ingestion of a medication—having too much of a drug in a person's system at once. This can happen if the dose taken exceeds the prescribed dose, either intentionally or accidentally. With certain medications, drug toxicity can also occur as an adverse drug reaction (ADR). In this case, the normally given therapeutic dose of the drug can cause unintentional, harmful and unwanted side effects. In some cases, such as with the drug lithium, the threshold between what is an effective dose and what is a toxic dose is very narrow. A therapeutic dose for one person might be toxic to another person. Drugs with a longer half-life can build up in a person›s bloodstream and increase over time. Additionally, factors such as age, kidney function, and hydration can strongly affect how quickly your body is able to clear a medication from your system.An adverse drug reaction (ADR) can be defined as 'an appreciably harmful reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product' (Aronson, J and Ferner, 2005 R) [3]. Since 2012, the definition has included reactions occurring as a result of error, misuse or abuse, and to suspected reactions to medicines that are unlicensed or being used off-label in addition to the authorised use of a medicinal product in normal doses (European Directive 2010/84/EU of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use).

Seminal research undertaken in the late 20th and early 21st century in the USA and the UK demonstrated that ADRs are a common manifestation in clinical practice, including as a cause of unscheduled hospital admissions, occurring during hospital admission and manifesting after discharge. The incidence of ADRs has remained relatively unchanged over time, with research suggesting that between 5% and 10% of patients may suffer from an ADR at admission, during admission or at discharge, despite various preventative efforts [22].

Chloroquine and hydroxychloroquine

These two antimalarial drugs have been getting a lots of attention, though their efficacy for the treatment of COVID-19 is still unknown. At least one clinical trial of chloroquine was stopped after it seemed to increased patient risk of heart fairlure. And the WHO temprorarily halted it trial due to safety concern. The reason why researchers are looking for this drugs as potential coronavirus treatments is that chloroquine and other drugs were able to block coronaviruses from infecting cells in the laboratory testing [8].

Metablock (LSALT peptide)

Dipeptidase 1 (DPEP1) is aglycoprotein that breaks up a number of substances, including leukotrienes, inflammatory mediators produced in white blood cells. Researchers at Arch Biopartners believe DPEP1 also recruits neutrophils, a type of white blood cell, to the lungs and liver during infection, causing inflammation. Metablok is DPEP1 inhibitor, and the company is studying its efficacy on lung and kidney inflammation in COVID-19 patients.

Methylprednisolone/corticosteroids

Methylprednisolone is a synthetic corticosteroid, which mimics how the body's hormones work to reduce inflammation. Corticosteroids are used to treat a plethora of conditions, from asthma to lupus to arthritis. Though they were used during severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks, the World Health Organization doesn't currently advise the use of corticosteroids for COVID-19, according to a February article from The Lancet. Clinical trials for glucocorticoid therapy are going forward at Peking Union Medical College Hospital and Tongji Hospital.

The main problem with the new virus is that there's no therapy for it, though plenty of potential cures are already in testing around the world. Some have shown promise in limited tests but need further scientific data. Others are vaccines that might eradicate the disease, but they need to pass through proper regulatory hoops that verify their efficacy and safety [9].

Additionally, Pfizer will test one of its antibiotics in coronavirus therapy that might be familiar to some people. Azithromycin, Zithromax or Z-Pak is the drug you've heard about on TV as a potential cure for COVID-19 if combined with hydroxychloroquine.

Recent advancement of therapeutics approaches for covid-19

The recent COVID-19 pandemic has alerted many researchers around the world to find treatment for this condition. COVID-19 is caused by a novel coronavirus species, named SARS-CoV-2. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), two other known viruses from the same genera, were identified in 2002 and 2012, respectively, causing serious respiratory ailments. COVID-19,

though a new virus, seems to have a similar pattern to SARS and MERS. Despite the differences in the mortality and epidemiological rates of these three diseases, the pattern of age-specific mortality is similar; and the mortality rates get higher as the age increases with zero fatality rate in children under n It has been shown that the potential first lines of defense against SARS are mediated through mannose-binding lectin as a pattern recognition molecule (PRM) of innate immunity. Additionally, interleukin (IL)-12 seems to play a vital role in SARS (13). IL-12 activation would lead to the induction of interferons (IFNs). IFN-γ is a key moderator in linking the innate immunity to adaptive immune responses IFNs are a group of cytokines, which communicate between cells against pathogens and have a critical role in the immune system, such as activating natural killer (NK) cells and macrophages, in addition to the flu-like symptoms of various diseases. There are three classes of IFNs: I (such as IFN-α and –β), II (IFN-γ), and III, all of which play roles against viral infections (Samuel CE, 2001). In SARS-CoV and MERS-CoV, the reaction to viral infections by type I IFNs is suppressed. Both CoVs use variant strategies to decrease type I IFN production. This dampening approach is highly associated with the disease severity and increased mortality. On the other hand, in the lethal cases of SARS-CoV or MERS-CoV infection, the increased influx of inflammatory cells is always observed. In a mouse model of SARS- CoV infection, imbalanced type I IFN and inflammatory cells were shown as the main causes of fatal pneumonia. Understanding the pattern of the immune system induction in adults and children in the CoV associated respiratory syndromes could help to find treatment strategies for these fatal diseases. Considering the lack of available data on COVID-19, SARS can be a helpful model in this regard. Because SARS-CoV-2 has the highest similarity in structure and nucleotide sequence to SARSCoV among other viruses of this family, showing 96% and 89.6% sequence identity in the proteins of their envelope and nucleocapsid, respectively [23].

In this section, we will review the recent advancement of therapeutic approaches based on the data obtained from bioinformatics tools and system biology approaches on the signalling pathway activated by the virus which will be validated based on the reviewed literatures from SARS, MERS, and COVID-19 to indicate how the dynamics of IFN-mediated antiviral response in adults, elderly, and children could determine the severity of the disease and treatment outcomes.

Protein interactions network reconstruction

In order to find the essential proteins and pathways in the gene set, the protein-protein interaction (PPI) network of the signature was extracted from the International Molecular Exchange Consortium (IMEx) protein interactions database through Network Analyst (https://www.networkanalyst. Network Analyst is a powerful and user-friendly analytics platform, which assists biologists in the interpretation of systems-level data. This tool was implemented to visualize and analyze the PPI network of top 100 DEGs. It is noteworthy that, in order to control the network size, the minimum network tool was selected amongst network tools, which keeps seed proteins and non-seed proteins that are crucial for network connections.

Gene set enrichment analysis

Gene set enrichment analysis is a method to interpret deferentially expressed genes (DEGs) in terms of the affected biological pathways and obtain information regarding signature. Gene ontology (GO) enrichment analysis on DEGs was performed by Enrichr (Chen EY, 2013) method at http://amp.pharm.mssm.edu/Enrichr/. GO knowledgebase) http://geneontology.org/ (contains comprehensive information about the function of genes in three main aspects, including biological process (BP), molecular function (MF), and cellular component (CC). In addition, pathway enrichment analysis for the top 100 DEGs was done by Enrichr as well. NCATS Bio Planet (https://tripod.nih.gov/bioplanet) (Huang R, 2019), Kyoto encyclopedia of genes and genomes (KEGG) (https://www.genome.jp/kegg/), and Reactome (https://reactome.org/) pathway databases were used for pathway enrichment analysis to assess the potential association of the signature with pathways [24].

Approaches to control COVID19

A systems biology perspective Induction of IFNs can play a key role in the body defense against CoVs infections, as supported by several studies mentioned in the following. Numerous studies have presented the success in defeating CoVs by the direct administration of IFNs. A combination of type I IFN and either IFN-γ or IFN-λ, was shown to synergistically inhibit the virus replication in vitro indicated that a combination of IFN-α and IFN-γ in vitro provided strong synergistic antiviral activities at much lower dosages of IFN than normally required. Lowering the dose of IFNs in combination therapy offers the advantage of reduction in undesired adverse re-

actions for the patients described the destructive effect of cytokine storm in adult mice after SARS-CoV infection. While IV injections of TNF-α was not beneficial, intraperitoneal IFN-γ injection showed a protective effect reported the in vitro superiority of IFN-β over -α and -γ, while suggesting the effectiveness of IFN-γ over IFN-α in Vero cell cultures of SARS-CoV infection and also reported the synergistic effects of IFN-γ and -β on Vero cells infected with SARS-CoV. Another study, demonstrated that IFN-α and -γ co-administration caused hyper-activated IRF-1 and STAT1, which finally led to a more robust antiviral symphony against virus replication. Altogether, it seems that combinational IFN therapy could significantly inhibit virus replication and overcome the increased response threshold of IFN induction that has been resulted by STAT1 inhibition in the immune cells by CoVs, especially in the elderlies.

Direct hit of viral replication and development of therapy on covid-19

The coronavirus genome is comprised of approximately 30,000 nucleotides. It encodes four structural proteins, Nucleocapsid (N) protein, Membrane (M) protein, Spike (S) protein and Envelop (E) protein and several non-structural proteins (NSPs). The M protein interact with envelop protein in the budding compartment of the host cell. The interaction between the virus and the host may be related to the glycosylation of the M protein and therefore, M protein believed to be central organizer of coronavirus assembly and determine the shape of viral envelop [25].

The S-protein is integrated over the surface of the virus, it mediates attachment of the virus to the host cell surface receptors and fusion between the viral and host cell membranes to facilitate viral entry into the host cell. The E-protein is a small membrane protein composed of approximately 76 to 109 amino-acid and minor component of the virus particle, it plays an important role in virus assembly, membrane permeability of the host cell and virus host cell interaction. A lipid envelop encapsulates the genetic material. Hemagglutinin-esterase dimer (HE) have been located on the surface of the viral. The HE protein may be involved in virus entry, is not required for replication, but appears to be important for infection of the natural host-cell. The capsid is the protein shell, inside the capsid, there is nuclear capsid or N-protein which is bound to the virus single positive strand RNA that allows the virus to hijack human cells and turn them into virus factories. The N protein coats the viral RNA genome which plays a vital role in its replication and transcription. The N-terminal of the N protein which is binding to genomic and sub-genomic RNAs in MHV and IBV Virions and process the viral replication and transcription. This is one of the important open research problems the developing of an effective drug targeting to prevent the contacts between N-terminal of N-protein and single positive RNA strand which can stop viral replication and transcription.

Coronavirus replication entails Ribosome frameshift and synthesis of both genomic and sub-genomic RNA species. The hallmark of SARS-COV-2 transcription is the production of multiple sub-genomic mRNA that contain sequences corresponding to both end of the genome. The mechanism of viral entry and replication and RNA packing in the human cell is mapped in figure 1. Following receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. A host type 2 transmembrane serine protease, TMPRSS2, facilitates cell entry via the S protein. Viral polyprotein (PPs) are synthesized once the virus is inside the cell. The PPs encoded for replicase-transcription complex (RTC). The virus then synthesizes RNA via its RNA-dependent RNA polymerase (RdRp). Structural proteins are synthesized leading to completion of assembly and release of viral particles. These viral life cycle steps provide potential targets for drug therapy (Figure 1). Promising drug targets include non-structural proteins (e.g., 3-chymotrypsin-like protease, papain like protease, RNA-dependent RNA polymerase), which share homology with other novel coronaviruses (nCoVs). Additional drug targets include viral entry and immune regulation pathways [26].

Development of therapy

Currently, there is no proven therapy for SARS-CoV-2, the cornerstone of care for patients with COVID-19 remains supportive care, ranging from symptomatic outpatient management to full intensive care support. However, there are 3 adjunctive therapies that warrant special mention are corticosteroids, anticytokine or immunomodulatory agents, and immunoglobulin therapy.

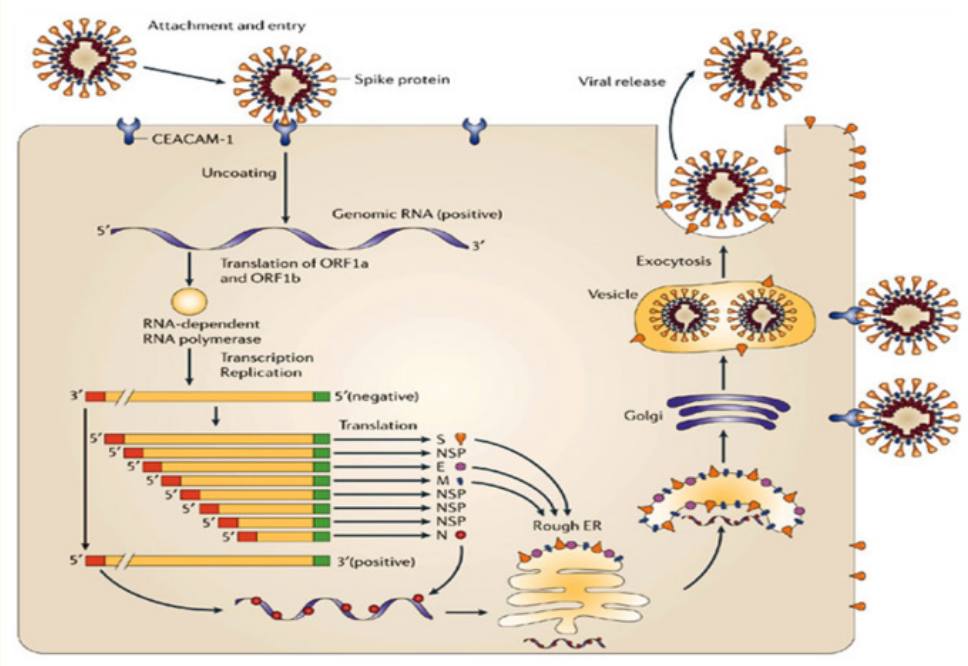

Figure 1: Summary of coronavirus replication and translation of viral proteins.

Source: Bergmann CC, Lane TE, and Stohlman SA., 2006.

Anticytokine or immunomodulatory agents

Monoclonal antibodies directed against key inflammatory cytokines or other aspects of the innate immunoresponse represent another potential class of adjunctive therapies for COVID-19. The rationale for their use is that the underlying pathophysiology of significant organ damage in the lungs and other organs is caused by an amplified immune response and cytokine release, or "cytokine storm. From the experience on the use of Tocilizumab, an FDA approved monoclonal antibody IL-6 antagonist to treat RA and cytokine release syndrome following chimeric antigen receptor T-cell therapy. Tocilizumab has been used in small series of severe COVID-19 cases with early reports of success. IL-6 appears to be a key driver of this dysregulated inflammation based on early case series from China. Thus, monoclonalantibodies against IL-6could theoretically dampen this process and improve clinical outcomes. Sarilumab, another IL-6 receptor antagonist approved for RA, is being studied in a multicenter, double-blind, phase 2/3trial for hospitalized patients with severe COVID-19 (NCT04315298) (Sanofi. Sanofi and Regeneron begin global Kevzara (sarilumab) clinical trial program in patients with severe COVID-19 [news release]). Other monoclonal antibody or immunomodulatory agents in clinical trials in China or available for expanded access in the US include bevacizumab (anti–vascular endothelial growth factor medication; NCT04275414), fingolimod (immunomodulator approved for multiple sclerosis; NCT04280588), and eculizumab (antibody inhibiting terminal complement; NCT04288713) (ClinicalTrials.gov. Accessed June 18, 2020.https://clinicaltrials.gov/).

Corticosteroids therapy

The rationale for the use of corticosteroids is to decrease the host inflammatory responses in the lungs, which may lead to acute lung injury and acute respiratory distress syndrome (ARDS). However, this benefit may be outweighed by adverse effects, including delayed viral clearance and increased risk of secondary infection. Although direct evidence for corticosteroids in COVID-19 is limited, reviews of outcomes in other viral pneumonias are instructive. Use of corticosteroid-based therapy to reduce inflammatory-induced lung injury has been described for patients with severe COVID-19, similar to the use of corticosteroids to treat severe acute respiratory syndrome (SARS) during the SARS outbreak in 2003. However, improper use of systemic corticosteroids can increase the risk of osteonecrosis of the femoral head (ONFH). While the efficacy of

corticosteroids in ARDS and septic shock more generally remains debated, Russell and colleagues argued that those most likely to benefit from corticosteroids are those with bacterial rather than viral infections. Therefore, the potential harms and lack of proven benefit for corticosteroids cautions against their routine use in patients withCOVID-19 outside an RCT unless a concomitant compelling indication, such as chronic obstructive pulmonary disease exacerbation or refractory shock exists.

Immunoglobulin or plasma therapy

Another potential adjunctive therapy for COVID-19 is the use of convalescent plasma or hyper-immune immunoglobulins. The rationale for this treatment is that antibodies from recovered patients may help with both free virus and infected cell immune clearance. Several convalescent patients are donating plasma against COVID-19 based on the positive results of another coronavirus. Surprisingly, it has preliminarily obtained favourable results in severe COVID-19 patients. On the other hand, the recombinant human monoclonal antibody is a straightforward path to neutralize viral load of COVID-19. CR3022 is a coronavirus specific human monoclonal antibody that can bind to the receptor-binding domain of COVID-19, this has the potential to be developed as candidate therapeutics of COVID-19 disease. Other monoclonal, m396, CR3014 antibodies, neutralizing COVID-19 that may be an alternative for the treatment of more severe cases [27].

As part of a 2015 systematic review, Mair-Jenkins and colleagues conducted a post hoc meta-analysis of 8 observational studies including 714 patients with either SARS or severe influenza. Administration of convalescent plasma and hyperimmune immunoglobulinwas associated with reduction inmortality(odds ratio,0.25[95% CI, 0.14-0.45]; I2 = 0%) with relatively few harms, although study quality was generally low and at risk of bias. In theory, the benefits of this therapy would accrue primarily within the first 7 to 10 days of infection, when viremia is at its peak and the primary immune response has not yet occurred. Although current commercial immunoglobulin preparations likely lack protective antibodies to SARS-CoV-2, this modality warrants further safety and efficacy trials as the pool of patients who have recovered from COVID-19 increases globally. Indeed, the first reported uncontrolled case series of 5 critically ill patients with COVID-19 treated with convalescent plasma in China was recently published. The most effective long-term strategy for prevention of future outbreaks of this virus would be the development of a vaccine providing protective immunity. However, long time of at least 12 to 18 months would be required before widespread vaccine deployment [28].

Despite the advantages and safety of plasma or convalescent therapy, it contain some adverse effects. Risks commonly associated with plasma transfusion include (1) transfusion-associated acute lung injury (TRALI), (2) transfusion-associated circulatory overload (TACO), and (3) allergic/anaphylactic reactions. Other less common risks include (1) transmission of infections, (2) febrile non-hemolytic transfusion reactions, (3) RBC alloimmunization, and (4) haemolytic transfusion reactions. A meta-analysis of studies that used convalescent plasma to treat SARS and influenza A (H1N1) reported no adverse effects beyond minor infusion reactions such as chills and fevers. Four critically ill patients with SARS-CoV-2 had no significant adverse events when treated with convalescent plasma and supportive care [29].

Substantial amount toxicity of drugs for treatment for Sars-cov-2

Table 3 summarized the pharmacology for selected proposed drugs used currently for the treatment of patient affected with SARS-COV-2. The table described the toxicity amount of the drugs administered, contraindication, drug-drug interaction and the special population used for the administration of the drugs including the pregnant woman.

Chloroquine and hydroxychloroquine

Dosing of chloroquine to treat COVID-19 has consisted of 500mg orally once or twice daily (Colson P, et. al., 2020; National Health Commission and State Administration of Traditional Chinese Medicine.2020). However, a paucity of data exists regarding the optimal dose to ensure the safety and efficacy of Chloroquine. Hydroxychloroquine dosing recommendations for SLE generally are 400mg orally daily (McFee, 2020). However, a physiologically based pharmacokinetic modeling study recommended that the optimal dosing regimen for hydroxychloroquine in COVID-19 treatment is a loading dose of 400 mg twice daily for 1 day followed by 200 mg twice daily. In contrast, alternative recommendations are made for 600mg total daily dose based on safety and clinical experience for Whipple disease. Further studies are needed extensively to delineate the optimal dose for COVID-19. Chloroquine and hydroxychloroquine are relatively well tolerated as demonstrated by extensive experience in patients with SLE and malaria. However, both agents can cause rare and serious adverse effects(<10%), in-

cluding QTc prolongation, hypoglycemia, neuropsychiatric effects, and retinopathy (Kalil AC. Treating COVID-19—off-label drug use, compassionate use, and randomized clinical trials during pandemics. Interview with David Juurlink. Coronavirus (COVID-19) update: chloroquine/ hydroxychloroquine and azithromycin. JAMA. March 24, 2020). Doses greater than 5 grams of chloroquine are associated with mortality due to ventricular dysrhythmias and hypokalemia. Cardiovascular collapse and profound hypotension can occur within 1–3 hours of overdose; sodium channel blockade results in QRS widening on ECG.

Neurologic effects include seizures and CNS depression. Oxidative stress can lead to hemolysis, particularly in patients with G6PD deficiency. Potassium channel blockade can result in prolonged QTc interval and torsades de pointes, and clinicians should avoid using QT prolonging agents if chloroquine toxicity is present. In this current pandemic, a man in Arizona died after ingesting chloroquine phosphate, a form of chloroquine used for treating aquariums, using it to self-medicate and cases of chloroquine poisoning have been reported in Nigeria. It is important to store chloroquine safely to avoid secondary harm. As little as 10 mg/kg of chloroquine in children, which could be 1–2 pills, requires medical evaluation; 27 mg/kg was the lowest fatal dose in toddlers [30].

No significant adverse effects have been reported for chloroquine at the doses and durations proposed for COVID-19. Use of chloroquine and hydroxychloroquine in pregnancy is generally considered safe (Chloroquine [database online].

Remdesivir and favipiravir

Remdesivir (Gilead) is a prodrug metabolized to an adenosine nucleotide analogue. It has demonstrated in vitro efficacy against SARS-CoV-2. Favipiravir (Toyama Chemical) mimics adenosine and guanine leading RNA-dependent RNA polymerase to make error-ridden non-functional viral genome progeny.

In the absence of available data on remdesivir or favipiravir toxicity, one can extrapolate from the toxicity reported for other nucleoside analogues. Dose administration of Remdesivir and Favipinavir vary based on indication presented by the patient, although 200 mg × 1, 100 mg every 24 h IV infusion has been recommended for remdesivir and available in 50mg/mL vial (reconstituted). Dose adjustments for Kidney is not recommended for GFR <30 for remdesivir uses. No kidney/hepatic dose adjustment currently recommended but holding doses may be considered if significant toxicities occur. Administration: 30-min IV infusion. Dose adjustment for favipinavir has been considered in Child-Pugh C, increased exposures observed in Child-Pugh class A to C and tablet administration can be crushed or mixed with liquid, bioavailability >95%.

Metabolic acidosis can occur with therapeutic use, usually after a month or more of treatment, though it has also been observed in acute overdose. Severe metabolic acidosis with elevated lactate is a toxicity of nucleoside analogues that has a high mortality. Peripheral neuropathy is a dose related, subacute phenomenon seen with stavudine, 2′, 3′- didehydro-2′, 3′-dideoxythymidine [32].

Lopinavir-Ritonavir

Lopinavir- Ritonavir are protease inhibitors prevent infected cells from forming competent new virions by binding to and inactivating viral proteases to halt viral replication. Viral proteases process the initial products of translation to make the final versions of viral proteins. Ritonavir is added to lopinavir as a pharmacokinetic booster ; ritonavir is a potent inhibitor of cytochrome CYP 3A4, the enzyme that inactivates lopinavir. The same regimen (lopinavir-ritonavir with ribavirin) was used as post-exposure prophylaxis for healthcare workers treating patients with severe Middle East Respiratory Syndrome (MERS, also caused by a coronavirus), which showed a 40% decreased risk of infection, and no severe adverse effects were reported [33].

Early experience in the treatment of SARS-CoV-2 suggests that patients treated with lopinavir-ritonavir commonly experience nausea and vomiting as well as mild transaminase elevations. Lopinavir-ritonavir seemed to hasten recovery in a case series of 10 hospitalized patients, but a larger randomized trial of 99 test subjects and 100 controls showed no difference in time to clinical improvement. In all three studies, many patients receiving the combination left the study due to nausea, vomiting, and diarrhoea. Acute overdose of protease inhibitors is uncommon, but a large overdose of more than 50 g of lopinavir-ritonavir was generally well tolerated and managed supportively. Ritonavir is a very potent inhibitor of CYP3A4 (Ki 0.59 ± 0.12μM), and may slow the metabolism of drugs which are substrates of CYP3A4, leading to potential dangerous drug-drug interactions.

Tocilizumab

Tocilizumab is a potential recombinant monoclonal antibody against IL-6 and currently is under investigation for the management of ARDS in patients with COVID-19. It was indicated that cy-

tokine release syndrome (CRS) and dominantly IL-6 play a central role in the pathophysiology of ARDS related to the novel 2019 coronavirus disease (COVID-19). Acute respiratory distress syndrome (ARDS) is the most devastating complication of SARS-CoV-2. Dose administration of tocilizumab is gives as 400 mg IV or 8 mg/kg × 1-2 doses. Second dose 8-12 h after first dose if inadequate response. Tocilizumab is available as IV infusion injection: 80 mg/4 mL (20 mg/mL); 200 mg/10 mL (20 mg/mL); 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to IV infusion. Common toxicity include Increase in upper respiratory tract infections (including tuberculosis), nasopharyngitis, headache, hypertension, increased AST, infusion related reactions. Major: Hematologic effects, infections, hepatotoxicity, gastrointestinal perforations, and hypersensitivity reactions [34].

Umifenovir (Arbidol)

Umifenovir (Arbidol) is an antiviral medication used for the treatment of influenza infection manufactured in Russia and China. The drug is claimed to inhibit viral entry into target cells and stimulate the immune response. Interest in the drug has been renewed as a result of the COVID-19 pandemic. A Clinical trials to evaluate its efficacy are also underway but some retrospective Study showed that Umifenovir Treatment Is Not Associated With Improved Outcomes in Patients with Coronavirus Disease 2019. Dose recommendation for Umifenovir is considered to be 200mg every 8 h by mouth 7-14 d. Available as (not in the US): 50-mg and 100-mg tablets, capsules and granules. Toxicity include Allergic reaction, gastrointestinal upset, elevated transaminases [36].

Novel mechanism and additional drug targets and future research

Coronavirus replication mechanism and mode of action of different repurposed or currently available therapeutic involved different action of the drugs that prevent it from producing or infecting the cells. The mechanism of different drugs ranges from initial viral entry mechanism whereby the virus S protein attaches itself to the ACE receptor of the host cell and get entry by the process of endocytosis and increase cytoplasmic pH of the infected cell, to the mechanisms that halt or reduces the production of viral RNA by obscuring the viral RNA polymerase and evades proofreading by viral exonucleases. The mechanism that inhibit proteases responsible for the cleavage of viral peptides in to functional protein for virus replication and packaging within the host. The process of viral RNA synthesis and the translation of proteins is associated with pH-dependent membrane stress, which can elicit adverse effects against immune and non-immune cells. If the viral replication cycle is not inhibited and infected cells are not eradicated, packed viruses will be disseminated to other cells in the host. Figure.1 shows a proposed acting points of anti-SARS-CoV-2 in the replication cycle of the virus and additional drug targets that help in the development of effective therapeutic drugs for SARS-COV2 [37].

Chloroquine and hydroxychloroquine

Chloroquine is a 4-aminoquinoline primarily used to treat malaria, an infectious disease caused by several Plasmodia species. Chloroquine concentrates in acidic environments, such as the digestive vacuole of Plasmodia spp. or the Golgi apparatus of human cells. Chloroquine prevents Plasmodia from crystallizing heme to hemozoin, leading to a build-up of heme that becomes toxic to the parasite. The Golgi apparatus is a collection of vesicles where post-translational modifications such as glycosylation occur.

Chloroquine freely diffuses into vacuoles. The acidic environment of the vacuole favours the protonated (charged) form, which cannot freely diffuse away (ion trapping), leading to a build-up of chloroquine in the vacuoles. Chloroquine alters the glycosylation of ACE2, which decreases the affinity of ACE2 for the coronavirus spike protein, reducing SARS-CoV-2nentry in vitro (Vincent M, 2005). Additionally, chloroquine and hydroxychloroquine inhibit the Toll-like receptor (TLR) pathway; but the TLR pathway is involved in pro-inflammatory cytokine signalling. Chloroquine was found to inhibit SARS-CoV-1 infection and he sequence and structure homologies between SARSCoV-1 and SARS-CoV-2 suggest that chloroquine could reduceSARS-CoV-2 infectivity.

Chloroquine and Hydroxychloroquine inhibit endocytosis of coronavirus from entering host cell. Spike(S) protein bind to the ACE receptor of the cell and endocytized in to the cell through endosome formation. The endosome transverse through the cytosome and fused with the lysosome where the virus can enter in to the lysosome allowing to infect the host cell. Chloroquine can block this process actively through entering in to the cell and permeate in to endosome and lysosome and alkalinize (increase the pH) the lysosome and endosome preventing it from being the acidity, this makes the lysosome and endosome less functioning or dysfunctional. Therefore, due to increase of endosomal and lysosomal pH, the endocytosis process that brings the virus in to the host cell will be inhibited and fusion of endosome and lysosome is stopped.

Therefore, chloroquine can increase endosomal and lysosomal pH and decrease or inhibit endosomal and lysosomal function endocytosis, thus inhibit coronavirus replication [38].

During a viral infection, the immune response is activated and the production and release of Pro-inflammatory cytokines, TNF_, IL-1, IL-6 and interferon-gamma (IFN) is increased. Chloroquine, However, blocks these events. Accordingly, chloroquine also prevents further deleterious mechanisms that may lead to acute respiratory syndrome, such as the alteration of tight junctions, the further release of pro-inflammatory cytokines, and increases in microvascular permeability.Chloroquine and hydroxychloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells. Chloroquine inhibits SARS-CoV-2 in vitro with a half-maximal effective concentration (EC50) in the low micro molar range. Hydroxychloroquine has in vitro activity with a lower EC50 for SARS-CoV-2 compared with chloroquine after 24 hours of growth (hydroxychloroquine: EC50 = 6.14 μM and chloroquine: EC50 = 23.90 μM) [39].

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Remdesivir

Remdesivir is a potential drug for treatment of COVID-19. It is a phosphoramidate prodrug of an adenosine C-nucleoside and a broad-spectrum antiviral agent synthesized and developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection. However, it has also shown activity against respiratory syncytial virus, Junin virus, Lassa fever virus, Nipah virus, Hendra virus, and the MERS and SARS coronaviruses. Remdesivir is metabolized into its active form, GS-441524, that obscures viral RNA polymerase and evades proofreading by viral exonuclease, causing a decrease in viral RNA production. The antiviral mechanism of remdesivir is a delayed chain cessation of nascent viral RNA (i.e Remdesivir inhibits RNA-dependent RNA polymerases, most likely through the delay of RNA chain termination in the cell. It is therefore one of the most promising compounds for treatingCOVID-19.

Favipiravir (Avigan, T-705)

Favipiravir has been developed as an anti-influenza drug and is licensed as an anti-influenza drug in Japan. One of the unique features of favipiravir is its broad-spectrum activity against RNA viruses, including influenza virus, rhinovirus and respiratory syncytial virus. Previous studies demonstrated that favipiravir is effective at treating infections with Ebola virus, Lassa virus and rabies, and against severe fever with thrombocytopenia syndrome. However, favipiravir is not effective against DNA viruses.

With regard to its mechanism, it is reported that favipiravir antagonizes viral RNA synthesis by acting as a chain terminator at the site where the RNA is incorporated into the host cell. By contrast, oseltamivir (Tamiflu), a neuraminidase inhibitor, blocks the cleavage of sialic acid and the subsequent entry of the virus into the cell. Importantly, favipiravir, unlike oseltamivir, does not seem to generate resistant viruses (Shiraki, K. and Daikoku, T, 2020). This property of favipiravir suggests a potential benefit in the treatment of critical infectious diseases such as COVID-19 (Figure 2).

Additional drug target and targeting potential entry mechanism of COVID-19

Promising drug targets include non-structural proteins (e.g., 3-chymotrypsin-like protease, papain like protease, RNA-dependent RNA polymerase), which share homology with other novel coronaviruses (nCoVs). Additional drug targets include viral entry and immune regulation pathways.

Dipeptidyl Peptidase 4 (DPP4; CD26)

It was reported that dipeptidyl peptidase 4 (DPP4) is a functional receptor for the emerging human coronavirus via S-protein, as well as ACE2. The interaction between the virus and the host cell membrane allows for viral S-protein-directed cell–cell fusion, and the resultant spread of viral infections. As another example relevant to drug repurposing and the ideal strategy for confronting COVID-19, the specific role of DPP4 on COVID-19 remains to be investigated. Further research is necessary to utilize DPP-4 as a therapeutic target for COVID-19 [41].

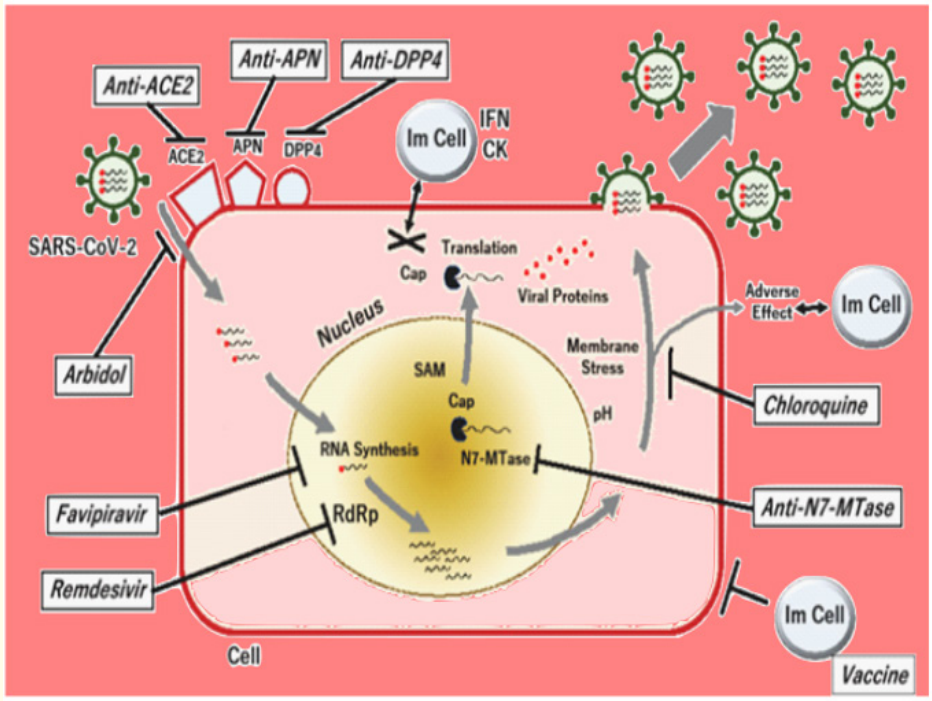

Figure 2: Proposed acting points of anti-SARS-CoV-2 in the replication cycle of the virus. When SARS-CoV-2 particles bind to their receptors, such as angiotensin-converting enzyme 2 (ACE2), aminopeptidase N (APN; CD13) and dipeptidyl peptidase 4 (DPP4; CD26), viral RNA is passed to the host cell, and RNA-dependent RNA polymerase (RdRp) produces viral RNAs. During RNAmethylation, the RNA cap is formed, which protects against the host innate immune response, which involves the secretion of interferons (IFNs) and cytokines (CKs). The viral (guanine-N7)-methyltransferase (N7-MTase) plays a critical role in RNA capping, using the methyl donor S-adenosylmethionine (SAM). The process of viral RNA synthesis and the translation of proteins is associated with pH-dependent membrane stress, which can elicit adverse effects against immune and non-immune cells. If the viral replication cycle is not inhibited and infected cells are not eradicated, packed viruses will be disseminated to other cells in the host. Proposed drugs and their possible acting points against COVID-19 are shown by bold lines.

Source: Asai, A., *et al*. 2020.

Aminopeptidase N (APN; CD13)

It was previously reported that aminopeptidaseN (APN) is involved in broad receptor engagement, which promotes the cross-species transmission of COVID-19 (Li,W.; Hulswit, R., *et al*. 2018).

Interestingly, previous studies identified APN as a surface marker for cancer stem cells in the human liver. Repurposing previous studies also allowed for the development of a poly-(ethylene glycol)-poly(lysine) block copolymer-conjugate (Ubenimex) that targets APN specifically. As drugs that can be repurposed, low doses of APN inhibitors, including Ubenimex or its derivatives, may be beneficial for inhibiting the spread of the virus.

Angiotensin converting enzymes 2 (ACE2)

ACE2, essentially acts as a port of entry that allows the coronavirus to invade our cells and replicate. Previous studies indicated that the angiotensin-converting enzyme 2 (ACE2) is the fuctional receptor for SARS-CoV, determined via single-cell sequencing and the structural analysis of proteins. The latter study demonstrated that the receptor-binding domain (RBD) of the viral spike (S)-protein in SARS-CoV-2 shows a strong interaction with human ACE2 molecules, despite its sequence diversity suggested that SARS-CoV-2 poses a significant public health risk for human transmission via the S-protein–ACE2 binding pathway. Interest-

ingly, the study showed that ACE2 was preferentially expressed by a small population of type II alveolar cells, and that males have higher ACE2 expression than females. The study also suggests that the binding of SARS-CoV-2 to ACE2 will increase the expression of ACE2. Studies in human and rodents showed that ACE2 expression is induced by treatment with ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), which are commonly used as antihypertensive drugs viz. Ramipril, Lisinopril. The expression of sodium-dependent neutral amino acid transporter B(0)AT1 depends on the presence of ACE2 in the respiratory tract. Given that COVID-19 includes symptoms such as fever (98%), cough (76%), dyspnea (55%) and fatigue/muscle pain (44%), its symptoms may berelevant to the respiratory expression of ACE2. High expression of ACE2 has been reported in small intestine. It was reported that SARS-CoV S murine polyclonal antibodies, targeting conserved S epitopes, inhibited SARSCoV-2 entry.

The role that ACE2 plays in COVID-19 is important in our understanding of the disease and could be used as a target for therapy. Drugs could be designed to block the receptor function of ACE2, but also there is promise in using the molecule itself in preventing entry of the virus into cells. Many therapeutic targets in the entry pathway via ACE2 have been reported so far, meaning ACE2 would therefore be a promising target for therapy of SARS-CoV-2.This would protect organs such as the lung, heart, kidney and intestine from extensive damage, and hopefully reduce mortality.

Pharmacokinetics of SARS-CoV-2

The pharmacokinetics of SARS-CoV-2 to appropriate therapeutics has been described in table 3 [45].

Drugs	Target
Chloroquine phosphate (Aralen/generic)	Blockade of viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Additional immunomodulatory effects through inhibition of cytokine production, autophagy, and lysosomal activity in host cells **Adult dose/administration** 500 mg by mouth every 12-24 h × 5-10 d. Available as: 250-mg tablets (salt); 500-mg tablets (salt); 500-mg tablets of chloroquine phosphate (salt) = 300-mg chloroquine base. Dose adjustments: Kidney: creatinine clearance <10 mL/min administer 50% of dose. Hepatic: No dose adjustments in hepatic impairment recommended; use with caution. Administration: Preferable to avoid crushing. If needed, may be crushed and mixed with jam, pasteurized yogurt or similar foods. **Contraindication** Hypersensitivity to chloroquine, 4-aminoquinolin compounds, or any component of formulation. Presence of retinal or visual field changes of any etiology(unless benefit outweighs risk) **Toxicity** Common: Abdominal cramps, anorexia, diarrhoea, nausea, vomiting. Major: Cardiovascular effects (including QTc prolongation), hematologic effects (including haemolysis with G6PD deficiency, use if benefit outweighs risks), hypoglycaemia, retinal toxicity, neuropsychiatric and central nervous system effects, idiosyncratic adverse drug reactions. **Drug-drug interaction** CYP2D6 and CYP3A4 substrate **Special population** May be used in pregnancy if benefit outweighs risks

Hydroxychloroquine sulfate (Plaquenil/generic).	**Target** Hydroxychloroquine shares the same mechanism of action as chloroquine **Adult dose/administration** 400 mg by mouth every 12 h × 1 d, then 200 mg by mouth every 12 h × 4 d; alternative dosing: 400 mg by mouth daily × 5 d or 200mg by mouth 3 times/d for 10 d. Available as: 200-mg tablets of hydroxychloroquine sulfate (salt) = 155 mg hydroxychloroquine base. Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution. Administration: Manufacturer does not recommend crushing tablets; however, some sources suggest that tablets can be crushed and dispersed with water OR compounded into an oral solution **Contraindication** Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivative, or any component of the formulation **Toxicity** Adverse drug reactions similar to chloroquine but less common **Drug-drug interaction** CYP2D6, CYP3A4, CYP3A5, and CYP2C8 substrate **Special population** May be used in pregnancy if benefit outweighs risks
Lopinavir/ritonavir (Kaletra).	**Target** 3CL protease **Adult dose/administration** 400 mg/100 mg by mouth every 12 h for up to 14 d. Available as: lopinavir/ritonavir, 200-mg/50-mg tablets; lopinavir/ritonavir, 100-/50-mg tablets; lopinavir/ritonavir 400-mg/100-mg per 5-mL oral solution (can be given via feeding tubes compatible with ethanol and propylene glycol, contains 42% alcohol). Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution in hepatic impairment. Administration: Food restrictions: Tablets, take without regard to meals; oral solution, take with food. Do not crush tablets; oral solution not recommended with polyurethane feeding tubes **Contraindication** Hypersensitivity to lopinavir/ritonavir or any of its ingredients, including ritonavir. Co-administration with drugs highly dependent on CYP4503A. Co-administration with potent CYP450 3A inducers **Toxicity** Common: gastrointestinal intolerance, nausea, vomiting, diarrhea. Major: Pancreatitis, hepatotoxicity, cardiac conduction Abnormalities. CYP3A4 inhibitor and substrate; CYP2D6 substrate; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 inducer. P-gp substrate; UGT1A1 **Drug-drug interaction** CYP3A4 inhibitor and substrate; CYP2D6 substrate; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 inducer. P-gp substrate;UGT1A1 inducer **Special population** May be used in pregnancy; avoid oral solution if possible due to ethanol content

Umifenovir (Arbidol)	**Target** S protein/ACE2, membrane fusion inhibitor **Adult dose/administration** 200mg every 8 h by mouth 7-14 d. Available as (not in the US): 50-mg and 100-mg tablets, capsules and granules. Dose adjustments: Kidney: no dose adjustment necessary. Hepatic: No specific recommendations available, caution in those with hepatic impairment. Administration: Bioavailability 40% **Contraindication** Known hypersensitivity to umifenovir **Toxicity** Allergic reaction, gastrointestinal upset, elevated transaminases **Drug-drug interaction** Metabolized by CYP3A4, monitor with strong inducers/inhibitors **Special population** Contraindicated in children <2 y of age (increased sensitivity)
Remdesivir	**Target** RNA polymerase inhibitor **Adult dose/administration** 200 mg × 1, 100 mg every 24 h IV infusion. Available as: 5-mg/mL vial (reconstituted). Dose adjustments: Kidney: Not recommended for GFR <30. No kidney/hepatic dose adjustment currently recommended but holding doses may be considered if significant toxicities occur. Administration: 30-min IV infusion. **Contraindication** Exclusion criteria based on specific protocols **Toxicity** Elevated transaminases (reversible), kidney injury. **Drug-drug interaction** Not a significant inducer/inhibitor of CYP enzymes, monitor with strong inducers/inhibitor **Special population** Safety in pregnancy unknown, currently recommended to avoid

Favipiravir.	**Target** RNA polymerase inhibitor **Adult dose/administration** Doses vary based on indication, limited data available. Available as (not in the US): 200-mg tablet. Dose adjustments: Kidney: no dose adjustment recommended, limited data available, Hepatic: Dose adjustment considered in Child-Pugh C, increased exposures observed in Child-Pugh class A to C. Administration: Tablet can be crushed or mixed with liquid, bioavailability >95% **Contraindication** Exclusion criteria based on specific protocols **Toxicity** Hyperuricemia, diarrhoea, elevated transaminases, reduction in neutrophil count **Drug-drug interaction** CYP2C8 and aldehyde oxidase inhibitor, metabolized by aldehyde oxidase and xanthine oxidase **Special population** Contraindicated during pregnancy, metabolite found in breast milk
Tocilizumab	**Target** IL-6 inhibition- reduction in cytokine storm **Adult dose/administration** 400 mg IV or 8 mg/kg × 1-2 doses. Second dose 8-12 h after first dose if inadequate response. Available as: IV infusion injection: 80 mg/4 mL (20 mg/mL); 200 mg/10 mL (20 mg/mL); 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to IV infusion. Dose adjustments: Kidney: No dose adjustments recommended in mild or moderate kidney impairment. Not studied in patients with severe impairment. Hepatic: No dose adjustments recommended (not studied); initiate based on benefit. Administration: Infuse over 60 min, should not be infused concomitantly in the same IV line with other drugs

	Contraindication Known hypersensitivity to tocilizumab or any components of the formulation. Caution in patients with neutropenia (<500 cells/μL) or thrombocytopenia (<50 000/μL) **Toxicity** Common: Increase in upper respiratory tract infections (including tuberculosis), Nasopharyngitis, headache, hypertension, increased AST, infusion related reactions. Major: Hematologic effects, infections, hepatotoxicity, gastrointestinal perforations, hypersensitivity reactions **Drug-drug interaction** In vitro data suggested that IL-6 reduces mRNA expression for several CYP450 isoenzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. May decrease levels of substrates **Special population** Safety in pregnancy unknown; may cause harm to the fetus

Table 3: Summary of Pharmacology for Select Proposed COVID-19 Treatments.

Source: (Sanders., *et al*. 2020).

Drugs of choice for pregnant woman affected with Covid-19

The lack of cellular structure of the virus contributes to its great variability, which also makes people still weak in antiviral treatment. Due to the lack of cell structure and the strong variability of virus, people still have difficulty in antiviral treatment. Since 2013, the FDA has approved only 12 drugs to treat viral infections, 10 for hepatitis C virus (HCV) and HIV, one for cytomegalovirus (CMV), and one for influenza virus (IFV). Currently, there is no specific drug for SARS-COV- 2. At present, people only have to choose existing drugs based on the past experience of antiviral and strive to develop vaccines or direct-acting antiviral drugs or host directed therapies at the same time. However, due to the presence of the fetus, many antiviral drugs are prohibited during pregnancy because of their proven teratogenicity. In addition, many prescription drugs lack reliable data to support their safety in treating pregnancy-related conditions. In fact, far fewer clinical drug trials are conducted during pregnancy than in any other major health field. Therefore, based on the existing evidence, some drugs have been proposed in order to treat pregnancy combined with COVID-19 as quickly, effectively, and safely as possible [42].

Chloroquine and hydroxychloroquine

As has been discussed, Chloroquine is a 4-aminoquinoline primarily used to treat malaria, an infectious disease caused by several Plasmodia species. Hydroxychloroquine is a derivative of chloroquine. Chloroquine phosphate, a FDA-approved antimalarial drug, has been used clinically for more than 70 years. Hydroxychloroquine is a new antimalarial drug developed by scientists on the basis of chloroquine in 1944. The difference between the two drugs is that one ethyl in chloroquine is replaced by one hydroxyethyl in hydroxychloroquine. Though the two drugs share similar therapeutic effects, the side effects of hydroxychloroquine are significantly less than that of chloroquine. At present, the main clinical applications are chloroquine phosphate and hydroxychloroquine.

We collected some evidences for the use of chloroquine in pregnancy combined with COVID-19. Although chloroquine is classified as class C in the FDA for pregnancy, the effect of chloroquine on pregnancy is proved to be mild. Some scientists believed that in the 20 years since the advent of chloroquine, an estimated 1 billion people have used chloroquine, including pregnant women.

They have not found any report of fetal damage, and the agencies responsible for malaria control in malaria-endemic areas have not banned the use of antimalarial by pregnant women and records in WHO do not show any adverse effects of chloroquine on pregnancy, childbirth, or newborns. In addition, regarding the pregnancy safety of hydroxychloroquine, Yusuf Cem Kaplan., *et al.* 2016 conducted a meta-analysis that included seven cohort studies and one randomized controlled trial, involving 1820 infants. The meta-analysis reported no significant increases in rates of major congenital (OR 1.13, 95% confidence interval (CI) 0.59, 2.17), craniofacial (OR 0.62, 95% CI 0.13, 3.03), cardiovascular (OR 1.06, 95% CI 0.29, 3.86), genitourinary (OR 1. 8, 95% CI 0.42, 4.53), nervous system malformations (OR 1.81, 95% CI 0.31, 10.52), stillbirth (OR 0.69, 95% CI 0.35, 1.34), low birth weight (OR 0. 69, 95% CI 0.21, 2.27), or prematurity (OR 1.75, 95%CI 0.95, 3.24). Based on this evidence, we speculate that hydroxychloroquine has the potential to be an effective drug in pregnancy with COVID-19 [43].

Interferons

Interferons are a family of naturally-occurring proteins that are made and secreted by cells of the immune system (for example, white blood cells, natural killer cells, fibroblasts, and epithelial cells). Three classes of interferons have been identified as alpha, beta and gamma. interferon beta-1a, currently in use to treat multiple sclerosis, and interferon alfa-2b are both under investigation as potential treatments for people with COVID-19 coronavirus disease, the deadly respiratory pandemic caused by the SARS-nCoV-2 virus. Essentially, when confronted with a virus, each cell shoots an emergency flare of interferon to tell the immune system to marshall its defenses. Interferon Beta 1a, specifically, activates macrophages that engulf antigens and natural killer cells (NK cells), a type of immune T-Cell. Those cells are integral in the innate immune system. The theory is, interferon may be able to make the immune system stronger by turning on dormant parts and directing them toward the defense against SARS-nCoV-2's assault.

Studies have shown that I-IFN has antiviral effects on various cell models, such as embryonic kidney cells (fRhK-4) of rhesus monkey and monkey kidney cells (Vero-E6), etc. In the study of infected macaques, preventive treatment of IFN-α significantly reduced replication of SARS virus, expression of viral antigen in type I alveolar epithelium, and lung injury [71]. The antiviral effect of IIFN was clearly demonstrated not only in animal experiments but also in human trials. In an open-label, non-randomized clinical trial of 22 SARS patients, nine were subcutaneous injected with I-IFN, and the results showed that all nine patients survived with fewer side effects. IFN-β1a shows stronger antiviral activity than IFN-α, and there was evidence that when IFN-α begins to show anti-SARS-CoV effects at 1000 IU/mL, recombinant human IFN-β1a is able to inhibit SARS-CoV activity strongly. Scientist conducted a meta-analysis to observe whether I-IFN has adverse effects on patients with primary thrombocytopenia (ET) during pregnancy. A total of 63 case reports of IFN-α direct exposure during pregnancy were included, of which 40 were diagnosed with ET, while 71 patients with ET not receiving any medication during pregnancy were taken as controls. The results showed that none of the 63 patients who received IFN-α during pregnancy had major malformations or stillbirths, and that IFN-α did not significantly increase the risk of malformations, miscarriages, stillbirths, or premature births. Thus, in the case of COVID-19 during pregnancy, IFN is expected to be effective and safe [44].

Lopinavir/ritonavir

Lopinavir and ritonavir are both HIV-protease inhibitors. typically, ritonavir is administered alongside other protease inhibitors to act as a competitive inhibitor of CYP3A4, thereby enhancing bioavailability and prolonging pharmacodynamics activity (Shepard's. Lopinavir and ritonavir. 2020). All beta coronaviruses contain two cysteine proteases that process viral polypeptides during replication, therefore lopinavir and ritonavir may offer some benefit in the adjunctive management of COVID-19.

Because lopinavir/ritonavir has a clear binding site with SARS-CoV, and the SARS-CoV-2 sequence shows a high homology with SARS-CoV-1, lopinavir/ ritonavir is strongly recommended for the treatment of COVID-2019. Using homologous modelling, Shen Lin., *et al*. 2020 established the structural model of protease C30 of SARS-CoV-2 and papain-like virus protease and then docked ritonavir and lopinavir with the protease model respectively. Through docking, 100 poses were found when docking ritonavir to CEP_C30, with the libdock score of the optimal pose 192.346. Eighty-eight poses were found when docking lopinavir to CEP_C30, with the libdock score of the optimal pose. The results suggest that the therapeutic effect of ritonavir on COVID-19 may be mainly due to its inhibition of coronavirus endopeptidase C30.

An open-label, randomized controlled trial 2014 involved 356 pregnant women infected with HIV. Lopinavir/ ritonavir or efavi-

renz was randomly administered at 12 to 28 weeks of pregnancy. Univariate and multivariate logistic regressions were used to analyse the potential risk factors for preterm labor. The results showed that lopinavir/ritonavir was not associated with an increased risk of preterm compared with efavirenz, except for nutr lopinavir/litonavir during pregnancy. Result showed that the prevalence of birth defects in infants with prenatal exposure to lopinavir/litonavir was not significantly different from that in internal or external controls. These data provide patients and clinicians with reliable information on the safety of lopinavir/ ritonavir in treating pregnant women with COVID-19. Thus, lopinavir/ritonavir is safer than other direct antiviral drugs. In addition, lopinavir/ritonavir is the preferred antiviral therapy for pregnancy with COVID-19, according to the second edition of the strategy recommendations for management of COVID-19 in pregnancy (published at Huazhong University of Science and Technology Union Hospital). So this drug deserves our full consideration in the treatment of COVID- 19 during pregnancy.

Remdesivir

Remdesivir is a novel, broad-acting antiviral nucleotide prodrug which effectively inhibits replication of SARS-CoV-2 in vitro and that of related coronaviruses including MERS-CoV in non-human primates (Shepard's. Lopinavir and ritonavir. 2020). A single small case series of six pregnant women exposed at various (unreported) stages of pregnancy whilst being treated for Ebola did not describe any adverse pregnancy outcomes.

Baricitinib

Baricitinib is a Janus kinase inhibitor which machine learning has identified as a potential drug for the treatment of COVID-19 by inhibiting the endocytosis of SARS-CoV-2 into pulmonary cells. A case report was located in the literature which described a patient with rheumatoid arthritis who was exposed to baricitinib from conception to 17 weeks. The outcome was a healthy infant born at 38 weeks. Tofacitinib is another Janus kinase inhibitor; although data are limited with approximately 60 exposed pregnancies published in a small number of uncontrolled case series crude rates of adverse pregnancy outcomes do not appear to be increased in comparison with their respective expected background rates

Drugs of choice for earlier detection and screening of woman affected with COVID-19

The current available screening and testing procedure for pregnant woman affected with COVID-19 are universal testing with nasopharyngeal swabs and a quantitative polymerase-chain-reaction test to detect SARS-CoV-2 infection in women who were admitted for delivery [46].

When it comes to treatment, specific drugs for COVID-19 have not been found at present, and taking old drugs for new use in treating COVID-19 has become an emergency method for the pandemic. Particularly, drugs that show superior maternal and fetal safety are worthy of consideration for pregnant women with COVID-19, such as chloroquine, metformin, statins, lobinavir/ritonavir, glycyrrhizic acid, and nanoparticle-mediated drug delivery (NMDD), etc. Pregnant women are susceptible to COVID-19, and special attention must be paid to the selection of drugs that are both effective for maternal diseases and friendly to the fetus. However, there are still many deficiencies in the study of drug safety during pregnancy, and broad-spectrum, effective and fetal-safe drugs for pregnant women need to be developed so as to cope with more infectious diseases in the future [47].

Drugs of choice for before the treatment and after the treatment and follow up of the treatment for COVID-19

Since there is no effective therapeutic drugs for covid-19 not only for pregnant woman but also for general public, existing antiviral drugs are being utilized to reduce the spread and management of the virus in affected patients. With immunocompromised status and physiological adaptive changes during pregnancy, pregnant women could be more susceptible to COVID-19 infection than the general population. As COVID-19 is rapidly spreading, maternal management and fetal safety become a major concern, but there is scarce information of assessment and management of pregnant women infected with COVID-19, and the potential risk of vertical transmission is unclear.

Since there is no effective drug, management is the best option in pregnant woman and the use of drug in pregnant woman need to be on the basis of solid evidence. Furthermore, Clinical trials are needed to prove the effectiveness of drugs and the effects on the fetus to establish a standardised treatment for pregnant women with COVID-19 (Management of Pregnant Women Infected with COVID-19, n.d.). More evidence of the safety of traditional Chinese medicine is also warranted. Additionally, the virus spreads mainly from person-to-person contact (Management of Pregnant Women Infected with COVID-19, n.d.).. Pregnant women can take the same steps as other people to protect themselves and should follow all the protocols and guideline set up by the CDC and the WHO and

need to consult their obstetrician–gynaecologist (ob-gyn) or other health care professional to ask how your visits may be changed [48].

Role of ACE inhibitor for SARS-CoV-2

SARS-CoV-2 appears not only to gain initial entry through ACE2 but also to subsequently down-regulate ACE2 expression such that the enzyme is unable to exert protective effects in organs. It has been postulated but still unproven that unabated angiotensin II activity may be in part responsible for organ injury in Covid-19. After the initial engagement of SARS-CoV-2 spike protein, there is subsequent down-regulation of ACE2 abundance on cell surface. Continued viral infection and replication contribute to reduced membrane ACE2 expression, at least in vitro in cultured cells.

SARS-CoV-2 is known to utilize angiotensin-converting enzyme 2 (ACE2) receptors for entry into target cells. Data are limited concerning whether to continue or discontinue drugs that inhibit the renin-angiotensin-aldosterone system (RAAS), namely angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

Concern arose regarding appropriateness of continuation of ACEIs and ARBs in patients with COVID -19 after early reports noted an association between disease severity and comorbidities such as hypertension, cardiovascular disease, and diabetes, which are often treated with ACEIs and ARBs. The reason for this association remains unclear.

The speculated mechanism for detrimental effect of ACEIs and ARBs is related to ACE2. It was therefore hypothesized that any agent that increases expression of ACE2 could potentially increase susceptibility to severe COVID-19 by improving viral cellular entry; however, physiologically, ACE2 also converts angiotensin 2 to angiotensin 1-7, which leads to vasodilation and may protect against lung injury by lowering angiotensin 2 receptor binding. It is therefore uncertain whether an increased expression of ACE2 receptors would worsen or mitigate the effects of SARS-CoV-2 in human lungs.The increased mortality and morbidity of COVID-19 in patients with hypertension is an association that has been observed in a number of initial epidemiological studies outlining the characteristics of the COVID-19 epidemic in China. Neither of these studies (15) adjusted for confounding variables and thus it remains unclear if this association is related to the pathogenesis of hypertension or another associated comorbidity or treatment. There has been a growing concern that this association with hypertension is confounded by treatment with specific antihypertensive medications: angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

The link with ACEIs and ARBs is because of the known association between angiotensin-converting enzymes 2 (ACE2) and SARS-CoV-2. ACE2 has been shown to be a co-receptor for viral entry for SARS-COV- 2 with increasing evidence that it has a protracted role in the pathogenesis of COVID-19. ACE2 has a broad expression pattern in the human body with strong expression noted in the gastrointestinal system, heart, and kidney with more recent data identifying expression of ACE2 in type II alveolar cells in the lungs. The concern that ACEIs and ARBs affect the severity and mortality of COVID-19 is 2-fold. One suggestion is that ACEIs could directly inhibit ACE2; however, ACE2 functions as a carboxypeptidase and is not inhibited by clinically prescribed ACEIs.

Furthermore, increase expression of ACE2 and increase patient susceptibility to viral host cell entry and propagation is another concern for the use of ACEIs. There has been considerable evidence in animal models as well as some evidence in humans showing increased expression of ACE2 in the heart, brain, and even in urine after treatment with ARBs; however, there is limited evidence showing changes Vaduganathan., *et al.* note that data in humans are limited, so it is difficult to support or negate the opposing theories regarding RAAS inhibitors. They offer an alternate hypothesis that ACE2 may be beneficial rather than harmful in patients with lung injury. As mentioned, ACE2 acts as a counter regulatory enzyme that degrades angiotensin 2 to angiotensin 1-7. SARS-CoV-2 not only appears to gain initial entry through ACE2 but also down-regulates ACE2 expression, possibly mitigating the counter regulatory effects of ACE2.

There are also conflicting data regarding whether ACEIs and ARBs increase ACE2 levels. Some studies in animals have suggested that ACEIs and ARBs increase expression of ACE2, while other studies have not shown this effect.

As controversy remains regarding whether ACEIs and/or ARBs increase ACE2 expression and how this effect may influence outcomes in patients with COVID-19, cardiology societies have largely recommended against initiating or discontinuing these medica-

tions based solely on active SARS-CoV-2 infection. Two clinical trials are currently in development at the University of Minnesota evaluating the use of losartan in patients with COVID-19 in inpatient and outpatient settings. (University of Minnesota. Losartan for Patients with COVID-19 Not Requiring Hospitalization (NCT04311177). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04311177?term=NCT04311177&draw=2&rank=1, 2020; University of Minnesota. Losartan for Patients With COVID-19 Requiring Hospitalization (NCT04312009). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04312009?term=NCT04312009&draw=2&rank=1). Results from these trials will provide insight into the potential role of ARBs in the treatment of COVID-19. in serum or pulmonary ACE2 levels. More relevant, the significance of ACE2 expression on COVID-19 pathogenesis and mortality is not specifically known.

The number of initial epidemiological studies outlining the characteristics of COVID-19 epidemic in China has been observed to show the increase in morbidity and mortality of covid-19 in patient. A new nationwide US observational study suggests that ACE inhibitors may protect against severe illness in older people with COVID-19, prompting the start of a randomized clinical trial to test the strategy.

In addition, a new meta-analysis of all the available data on the use of ACE inhibitors and angiotensin-receptor blockers (ARBs) in COVID-19 infected patients has concluded that these drugs are not associated with more severe disease and do not increase susceptibility to infection.

The observational study, which was published on the MedRxiv preprint server on May 19 and has not yet been peer reviewed, was conducted by the health insurance company United Heath Group and by the Yale University School of Medicine, in New Haven, Connecticut(ACE Inhibitors and Severe COVID-19: Protective in Older Patients? | MDedge Cardiology, n.d.).

The investigators analysed data from 10,000 patients from across the United States who had tested positive for COVID-19, who were enrolled in Medicare Advantage insurance plans or were commercially insured, and who had received a prescription for one or more antihypertensive medications.

Results showed that the use of ACE inhibitors was associated with an almost 40% lower risk for COVID-19 hospitalization for older people enrolled in Medicare Advantage plans. No such benefit was seen in the younger commercially insured patients or in either group with ARBs [49].

Recent updates on COVID-19

Since the outbreak of COVID-19 pandemic, efforts have been made sincerely in order to develop effective therapeutic for SARS-COV-2 and other member of Coronavirus family. However, despite all these efforts, till date there are no licensed vaccines or therapeutic agents (i.e., antivirals and monoclonal antibodies) indicated for the prevention or treatment of SARS-COV2. Although a lot of clinical trials are ongoing, but some are still at their early stage and scientists are making a lot of work in identifying a therapeutic candidate of the virus.

Recently, after virtually screening 640 existing drug compounds, researchers were able to reveal some drugs that believed to be the candidate for SARS-COV-2. One of the candidate revealed by researchers is PC786 that potentially target several SARS-COV-2 receptors, making it a candidate to fight covid-19. According to the new study, virtually screening compounds to model their interactions with the SARS-CoV-2, the virus causing COVID-19, may not only enable scientists to more easily identify antiviral drugs that work against the virus, but also inform the search for viable vaccine candidates [50].

The study which was conducted by researchers at Uppsala University, Sweden, published in Science Advances on June 24, 2020 showed that by screening for interactions with certain structural domains and active sites on the virus, this structure-based approach allowed them to identify existing drugs that can be repurposed, including therapies developed to treat MERS-CoV, SARS-CoV, Ebola, and HIV. They highlight that this approach may also assist with the development of new drugs and protein-based COVID-19 vaccines with fewer experiments and higher reliability than traditional methods. The researchers say that information about SARS-CoV-2 reported from its recent genome sequencing has revealed key targets for drugs and vaccines, including the Spike (S) protein complex, which helps to mediate viral entry into host cells, as well as the main protease, an enzyme that enables viral replication and transcription. To test how these elements of the virus' structure may be used to search virtually for prospective drugs, PhD student from Uppsala University Pritam Kumar Panda and colleagues computationally screened 640 antiviral compounds from a database against the S protein and main protease using AutoDock Vina, an open-source programme for identifying the 'best fit' orientation of

a molecule that binds to a protein [21].

The researchers then used two additional programs, UCSF Chimera and Discovery Studio Visualizer, to analyse these molecular orientations [35]. The researchers found that an antiviral polymerase inhibitor PC786 targets several SARS-CoV-2 receptors with high affinity, making it a standout among the antiviral drugs they studied.

Maurya., *et al*. and also identified several additional anti-viral, anti-protease, and antiinfectious compounds with strong binding affinities to the NSP10/NSP16 methyltransferase and main protease of SARS CoV-2 revealing a number of drugs that may be candidates for further research in efforts to fight COVID-19 [31].

The researchers then used two additional programs, UCSF Chimera and Discovery Studio Visualizer, to analyse these molecular orientations [12,20]. The researchers found that an antiviral polymerase inhibitor PC786 targets several SARS-CoV-2 receptors with high affinity, making it a standout among the antiviral drugs they studied.

Panda and the researchers also identified several additional antiviral drugs with strong binding affinities to the S protein and main protease, revealing a number of drugs that may be candidates for further research in efforts to fight COVID-19.

Researchers also have developed 'nanosponges' cloaked in lung cell membranes and macrophage membranes which they found could attract and neutralise COVID-19 in cell cultures.

According to a new study, nanoparticles cloaked in human lung cell membranes and human immune cell membranes can attract and neutralise the SARS-CoV-2 virus in cell culture, causing the virus. The technology was developed by engineers at the University of California (UC) San Diego and tested by researchers at Boston University, both US. Dubbed 'nanosponges', the researchers found that the particles can soak up the virus which is causing the COVID-19 pandemic, to lose its ability to hijack host cells and reproduce. In cell culture experiments, the team led by Quangzhe and his colleques demonstrated that both types of nanosponges (fragments of the outer membranes of lung epithelial cells and macrophage membrane) caused the SARS-CoV-2 virus to lose nearly 90 percent of its viral infectiousness in a dose-dependent manner. At a concentration of 5mg per ml, the lung cell membrane-cloaked sponges inhibited 93 percent of the viral infectiousness of SARS-CoV-2. The macrophage-cloaked sponges inhibited 88 percent of the viral infectiousness of SARS-CoV-2.They also revealed that the nanosponges had angiotensin-converting enzyme 2 (ACE2) and CD147, which are the virus' natural targets it uses to gain entry into cells, projecting outward from the polymer core. Furthermore, instead of targeting the virus itself, these nanosponges are designed to protect the healthy cells the virus invades. Tested in mice, the team found that their technology did not have any short-term toxicity. The researchers note that nanosponges cloaked with fragments of the outer membranes of macrophages could have an added benefit: soaking up inflammatory cytokine proteins, which are implicated in some of the most dangerous aspects of COVID-19 and are driven by immune response to the infection. From the perspective of an immunologist and virologist, the nanosponge platform was immediately appealing as a potential antiviral because of its ability to work against viruses of any kind. This means that as opposed to a drug or antibody that might very specifically block SARS-CoV-2 infection or replication, these cell membrane nanosponges might function in a more holistic manner in treating a broad spectrum of viral infectious diseases," said co-first author Associate Professor Anna Honko, at Boston University.

A new drug candidate named PL8177 has been developed to treat COVID-19 and has shown success in pre-clinical trials. The drug candidate PL8177 reduced inflammation, protected lung tissue and reduced lung fibrosis in pre-clinical models with symptoms of COVID-19(PL8177 Shows Success as COVID-19 Therapy in Pre-Clinical Trials, n.d.).

According to Palatin Technologies, Inc., which developed PL8177, says it could help patients with hypoxemic respiratory failure with or without acute respiratory distress syndrome (ARDS), associated with COVID-19. The drug is a potent and selective melanocortin 1 receptor (MC1r) agonist(PL8177 Shows Success as COVID-19 Therapy in Pre-Clinical Trials, n.d.).

The company stated that the candidate demonstrated success and had positive results in multiple pre-clinical inflammatory disease models and a lung injury model, which showed the ability of PL8177 to reduce inflammation, protect lung tissue and reduce lung fibrosis.

"We are excited about PL8177's potential to be part of the solution to this unprecedented global public health crisis," said Dr Carl Spana, President and Chief Executive Officer of Palatin. "What is

differentiating about PL8177 is its potential to reduce the inflammation associated with progressive COVID-19 disease and to reduce lung fibrosis, which can compromise patient lung function after recovering from the viral infection".

Palatin has now submitted a preliminary proposal to the US Biomedical Advanced Research and Development Authority (BARDA) on this programme and submitted a pre-Investigational New Drug (pre-IND) package to the Division of Pulmonary, Allergy and Critical Care (DPACC) of the US Food and Drug Administration (FDA).

Based on advice from DPACC, the company is planning to submit an IND in the third quarter of 2020 and planning a Phase II clinical trial initiation in the fourth quarter 2020 to test the drug against COVID-19. Required pre-clinical and Phase I safety studies are complete and support the safe use of PL8177 in a Phase II clinical study(PL8177 Shows Success as COVID-19 Therapy in Pre-Clinical Trials, n.d.).

Limitations

Despite the enormous efforts put in place to produce effective therapeutic drugs against the current pandemic of COVID-19, yet no potential drug has been proven to be the therapeutic candidate of the virus. The most effective long-term strategy for prevention of future outbreaks of this virus would be the development of a vaccine providing protective immunity. However, a minimum of 12 to 18 months would be required before widespread vaccine deployment.

The role of ACE Inhibitor in the treatment of covid-19 has been a subject of argument as some people thinks that it will increase the susceptibility of patients affected with covid-19, as SARS-CoV-2 appears not only to gain initial entry through ACE2 but also to subsequently downregulate ACE2 expression such that the enzyme is unable to exert protective effects in organs.

The available drugs for covid-19 treatment have been found to cause toxicity at some patient especially those with cardiovascular diseases and has contraindications, therefore, effective therapeutic of sars-cov2 need to be develop to eliminate this devastating outbreak. The current ongoing clinical trial need to assess the effectiveness of the proposed drugs which are being used for the treatment of covid-19. Another limitation the study is that, some published treatment data or clinical trial results are derived from small clinical trial (some with not more than 300 patients), therefore, introducing higher risk of bias regarding the magnitude of treatment effect size.

Conclusion

Although specific treatments, including vaccines, have not yet been developed for COVID-19, effective prevention methods are now recommended on a global scale. Accordingly, to overcome with this pandemic, developing specific inhibitors for viral entry and replication, as well as drug repositioning, will be necessary. As above, several clinical trials and drug repositioning studies are currently ongoing and this and drug repurposing ongoing clinical trials should be based on the specific guidelines and Specific regimen for therapeutic efficacy of the drugs. Eventually, new studies will allow us to better exploration and control of this pandemic and identify new treatments.

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Conflicts of Interest

The authors declare no conflicts of interest.

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