DRUG DISCOVERY

A novel and Emerging Coronavirus Infection: Repurposing and Scale of Advances of Therapeutics, Imunotherapeutics and Vaccine Development

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ABSTRACT

A new coronavirus (nCOVID-19) has appeared in China for the first time, inducing various effects in humans and strongly linked to those induced by SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome). Several cases of this infection with the coronavirus respiratory syndrome have also been identified in over 215 countries. More than 16,482,747 cases of coronavirus disease 2019 have been recorded since December 2019 and about 653,325 deaths around the world have occurred. In the USA, Brazil, India, Russia, South Africa, Mexico, Peru, Chile, Spain, United Kingdom, Italy, Germany and France, most cases have been registered. This public health epidemic has been the emergence of this emerging illness which threatens to propagate exponentially across the globe. The accepted cases are subdivided into four groups dependent on clinical evidence, which involve mild, moderate, serious and critical instances. Of the active cases, approximately 1% were seriously/critically ill and 99% were in mild conditions. The infection fatality incidence was roughly 6%. This analysis focuses on knowledge currently available about COVID-19's etiology, clinical signs, diagnosis, and mode of action. In addition, according to current evidence, we provide a summary of the

diagnosis methods and treatment for this condition. This review information will help the physician identify and manage COVID-19 effectively.

Keywords: nCOVID-19; Vaccine; Therapeutics

1. INTRODUCTION

Epidemiology

Novel corona virus disease 2019 (COVID-19) a global pendemic pandemic began in Wuhan city of china on December 2019.[1] It initiated infection in 2nd January 2020, near about 41 Patients with tiredness, fever, cough and myalgia admitted in the health centre of China. Later every patient associated with severe pneumonia confessing to the intensive care unit (ICU) because of serious respiratory disorder (30%) and 6 of them died.[2] Within a short duration, these new genetic variants of Beta CoV grow over a wide geographic area. As per WHO, 2020 the rate of COVID-19 infection spread over 200 countries and territories. Worldwide 83,652 people affected and the number of fatalities is over 3,000 on February 28, 2020. Further, the rate of infection increased, around 1,285,257 people affected and fatality rate approximately 5.4% (70,344/1,285,257) on April 6, 2020.[3] Initially, Chinese patients (72,314) with suspected, confirmed, and symptom-less conditions revealed various crucial epidemiological aspects of COVID-19. Out of 1,023 mortality cases, most patients were above 60-80 years of age (20.3%). However, children within 0-9 years old reported with few cases. Compared to females, males are more prone to this disease (China 1.06:1, Hubei 1.04:1 and Wuhan 0.99:1, based upon population scales).[4,5]

Taxonomy, Structure, Genomic Characteristics and CoVs Replication Pathway

Coronaviruses (CoV) are enveloped RNA virus belonging to family Coronaviridae, with variable sizes (80 to 120 nm in diameter).[6] International Committee for Taxonomy of Viruses (ICTV), a CoV Study group reported about four genera of Coronaviridae that is α, β, Γ, and Δcoronavirus.[7] The group/genus α contains HCoV-NL63 and HCoV-229E, CoV of humans. The group/genus β comprised of (A, B, C, and D) lineages that carry HCoV-OC43 and HCoV-HKU1 (lineage A), SARS-CoV (lineage B), and MERSCoV (lineage C). Particularly, HCoV-229E and HCoV-OC43 have acknowledged in 1960, develop common cold symptoms. HCoV-NL63 genomic sequence was isolated from a child with an age of only 6 months and identified. Γ and Δ coronavirus find out in mammal contain avian coronaviruses not discovered in humans.[8]

5-Methylguanosine cap at the beginning are the constituent of SARS-CoV (SARS-CoV-2) and MERS-CoV genomes, a total of 6-10 genes in between and poly-A tail. It translated by two open reading frames having different overlapping followed by ribosomal frame shifting and converted into two uncoated non-structural polyproteins (nsps).[9] Glycoproteins formed through the process of glycosylation by Golgi apparatus. At Spike 1 (S1) area of the receptor-binding domains (RBD) SARS-CoVs species use the N-terminus and other species uses C-terminus. Cleavage of S protein by host transmembrane protease, cathepsin, transmembrane serine protease type 2 (TMPRRS2), and angiotensin-converting enzyme 2 (ACE2) receptor, that manages the entry of SARS-CoV (SARS-CoV-2) and HCoV-NL63 viruses. Proteolytic S protein cleavage accompanied by the fusion of plasma membrane or by acidified endosomes to facilitates entry of the viral genome towards the host cell.[10]

Viral S protein on interacting with host ACE2 results in downregulation of ACE2a through a negative feedback loop mechanism that controls its angiotensin I substrate towards its enzyme, ACE and increased its activity. Thus, enhanced ACE activity automatically elevates angiotensin II levels that, followed by its receptor binding angiotensin II receptor, type 1(AGTR1A), increase pulmonary vascular permeability.[11] Whereas, cell adhesion molecule-1 (CEACAM-1) and dipeptidyl peptidase 4 (DPP4) receptor responsible for MERS-CoV binding.[12]

Inside the host cell, virion genomic RNA responsible for the movement of the replicase gene, which encodes replicase-transcriptase complex (rep1a and rep1b) with its co-terminal polyproteins (pp1a and pp1ab). CoVs species use smooth sequence (50-UUUAAAC- 30 from the rep1a to rep1b) with a pseudo-knot of RNA for frame-shifting of the ribosome during translation.[13] Replicase polyproteins in connection with nsps responsible for cleavage of two or three proteases that encoded by CoVs. Encodeing of papain-like proteases (PLpro) done inside nsp3 in SARS and MERS, while in other serine protease (Mpro) encoding done inside nsp5.[14] Replicase-transcriptase complex (RTC) formed by the assembled nsps via its RNA-dependent RNA polymerase (RdRp) that builds a controlled status for viral RNA synthesis.[15]

Finally, structural proteins with S, E, and M possess a translation of virus and that push into the endoplasmic reticulum (ER) in the cytoplasm.[16] Encapsidation (enclose viral nucleic acid within a capsid) of viral genomes performed by mature virions N, M and E protein and produce the CoV envelopes, respectively. On the other hand, nucleocapsid binds to N and M protein and accelerates

the formation of virus-like particle (VLP) that complete virion construction and the M protein binds to the nucleocapsid and encourage the completion of virion assembly.[17, 18] Next, The virions move towards the cell surface membrane in the presence of lipid bilayer vesicles and ultimately released by the process of exocytosis. However, in some CoVs the S protein, does not accumulate into virions, transport towards the surface of the cell and conciliates fusion between infectious cells and the adjacent uninfectious cells, that leads to the establishment of multinucleated giant cells, not detected or counteract by virus-specific antibodies but permit the virus to outspread inside an infected organism.[18]

However, variation in ACE2 expression level and frequency of allele in-between populations is the main consideration. Uniform responsiveness for SARS-CoV-2 among individuals can be another underlying cause for rapid growth over different human populations and continents.

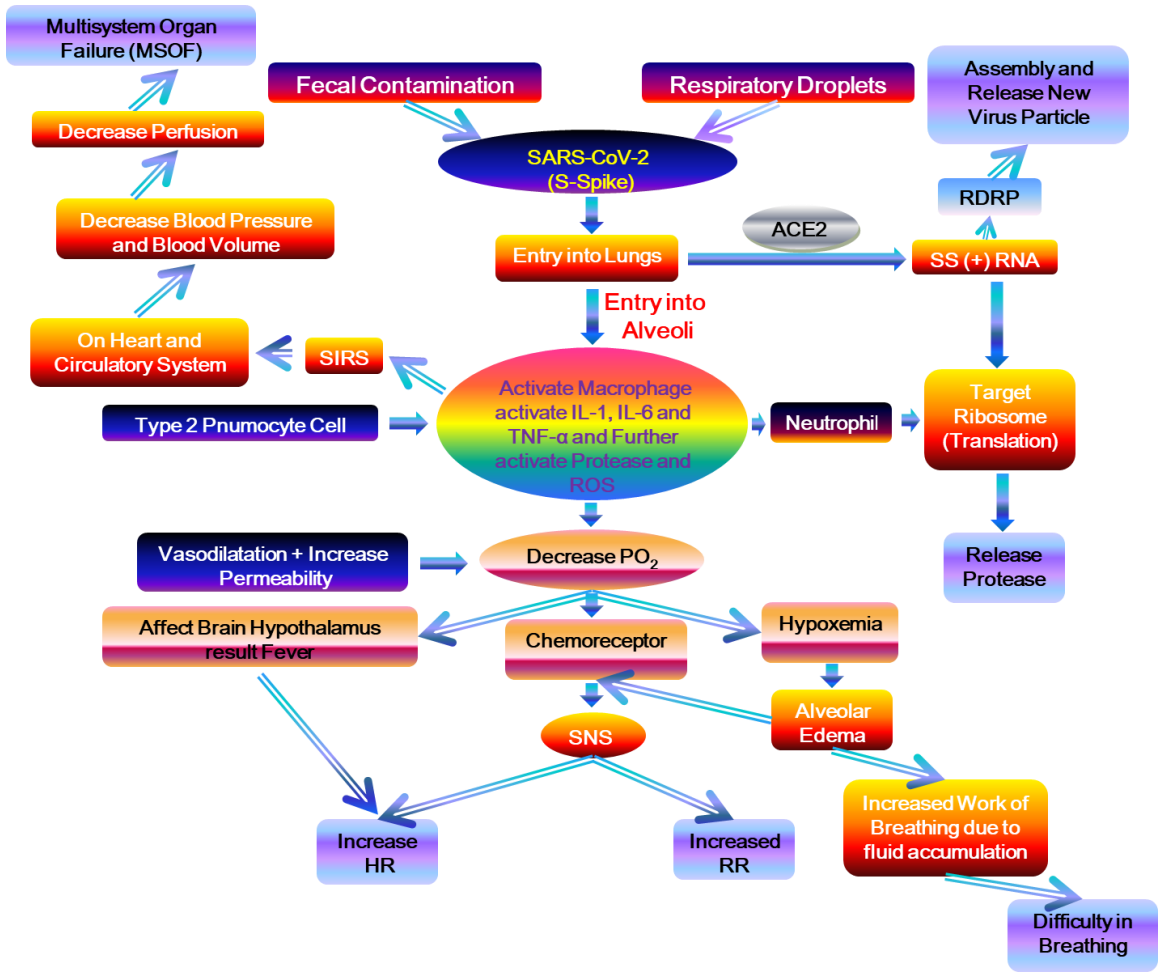

Figure 1: Physiological mechanism of SARS-CoV-2 in schematic illustration.

Pathogenesis of CoVs

Earlier notions indicate that mild and limited infections of the respiratory system in humans only cause by CoVs, however, an upsurge of SARS and MERS CoVs alter this notion.[19] CoVs cause lower respiratory tract infection and HCoV-NL63 is responsible for intense laryngotracheitis (croup) in humans, whereas HCoV-229E is obvious for mice infection.[20] nCoV-19 and HCoV-OC43 have logical genetic variation while HCoV-OC43 can infect mice and several herbivorous species. It has been reported that multiple sclerosis (MS) develop by CoVs of humans. An elderly person with cardiovascular disease, hypertension, diabetes, chronic bronchitis, chronic obstructive pulmonary disease, cerebral infarction, Parkinson's disease, and cancer mainly affected by nCoV-19.[21-23]

The peoples in this era have felt the appearance and infestation of 3 formerly unidentified coronaviruses. SARS-CoV is responsible for the development of SARS (severe acute respiratory syndrome) was identified in 2003, flares up in the Guangdong territory of China. HCoV-EMC (human coronavirus EMC) first found out in an old man in Bisha with 60 years of age, belong to Saudi Arabia (KSA), and another in Doha, Qatar passed away due to community gained pneumonia and failure of kidney on 23rd of September 2012, communicated by the World Health Organization (WHO).[24] Since then, several tragedies have been communicated

in Europe and the Middle East, and later renamed by International Committee on Taxonomy of Viruses (ICTV) as Middle East respiratory syndrome coronavirus (MERS-CoV).

Bamboo bats, MERS-CoV reservoir, discovered in Hong Kong in 2007, phylogenetically resemblance to other C lineage betacoronaviruses, Japanese and Pipistrellus Tylonycteris bat (Pi-BatCoVHKU5 and Ty-BatCoV-HKU4).[25,26] MERS-CoV genomic analysis showed its genome size constitute of 30, with 106 bases having S and RdRp genes. There are also 90% amino acid sequence with Ty-BatCoV-HKU4 and 70% amino acid sequence that resemble with Pi- BatCoV-HKU5.[27, 28] RdRp analysis manifested, MERS-CoV is a forefather of nCoV (novel coronavirus) with lineage C betacoronaviruses declared in December 2019 and officially named SARS-CoV-2.[28] Till now, several animals hypothesized as the reservoir for SARS and MERS CoVs, but still now animal sources are not confirmed. It has been reported that 'wet markets' placed in South China with living wild animals is the beginning place for breakouts COVID- 19. However, snakes as a viable source for nCoV- 19 are under disputed condition. Some animals like canine, equine, porcine, bovine, and camel also conspicuous in Betacoronaviruses. Horseshoe bats are considered as a prime reservoir for this nCoV, and the mid hosts responsible for the transmission of the virus to human are dromedary camel and palm civet for MERS-CoV and SARS-CoV, respectively. Also, it has reported that, other wild animals or via pangolin (Manis javanica) nCoV- 19 may communicate to humans, expectedly link to the wet market of Wuhan.[29] It is suggested that the SARS epidemic scenario similar to the arrival of COVID 19 as an interspecific transmission, from bats to other animals and then ultimately to humans.

Generally, SARS-CoVs infect the lungs epithelium and also penetrate into dendritic cells and macrophages of humans. Infected cells of SARS-CoV-2 liberate interferon gamma-induced protein 10 (IP10), macrophage inflammatory protein (MIP) 1α, monocyte chemoattractant protein 1 (MCP1), granulocyte-colony-stimulating factor (GCSF), tumor necrosis factor- alpha (TNFα) and interleukins (IL2, IL7, IL10), like several proinflammatory cytokines and mediator for inflammatory and immune suppressive diseases.[30-32]

However, conveyance of SARS-CoV-2 from human-to-human occurs through direct contact with infected individuals, mainly in the group and in-between family members, signifies spread of pathogen before the beginning of symptoms. SARS-CoV and SARS-CoV-2 average contagious period of 1.1 to 1.2 h with half-lives were alike in aerosols.[33] As a reflection of SARS-CoV, air-borne, and fecal–oral communication, the chance of SARS-CoV-2 may not be lay down.

Human to Human contagious infection spread worldwide announced as Pandemic disease. Close to other RNA viruses, this family of virus specified with remarkable genetic variation and the top rate of recombination empower them to be comfortably disseminated between humans and animals globally. Thus, many CoVs without producing life-threatening diseases exist inside human and animal society. Sometimes, recombination of the viral gene inside random transitional hosts starts infectious strains which are tremendously morbific for the human being.[34] SARS-CoV-2 possesses a unique characteristic that quickly grows around the world. The under way CoV warning that came out in China quickly proliferate to other countries and WHO already announce it as a world health disaster or pandemic.

General Clinical characteristics of CoV and COVID-19

CoV may contaminate humans and animals and develop certain complications of the respiratory system and gastroenteritis.[35, 36] Lakhs of human death occurs because of nCoV-19 has already identified in between January-august 2020.

Travel histories to the endemic location with close contact records are important parameters for patients identification.[37] Fever (83–95%), shortness of breath (19–53%), cough (59–80%), and muscle ache (11–42%), is the standard sign of COVID-19 as like as SARS and MERS. However, several patients experience headache, confusion, rhinorrhea and sore throat just before the beginning of a fever.[23] Some cases having coughing up of blood (hemoptysis) and recently a large proportion of patients found relatively asymptomatic.[22, 35] Usual or lower white blood cell counts (leucopenia), lower platelet count (thrombocytopenia), including the elevated C-reactive protein level provoke symptom of rheumatoid arthritis may experience by patients with COVID-19.[2, 22] In few patients, dyspnoea appears within 5–13 days following the onset of illness, while in others, it may be absent.[35] Inadequacy of breath and ischemic hypoxia in sick patients can rapidly advance into severe respiratory distress syndrome (17–29%), acute infectious septicemia and dysfunction of different organs in 8 days following manifestation.[22,38] Angiotensin-converting enzyme 2 (ACE2) a principal receptor of SARS-CoV-2 exhibited in the gastrointestinal epithelial cells of human beings, while gastrointestinal shedding of virus and transmission through fecal–oral route is sensible. However, negative was reported for nasopharyngeal tests, but positive results for the rectal swabs.[36, 39] Stool specimen of infected patients detected with live virus strongly narrates stool transmissible effect even after the discharge of patients for a prolonged time. Thus, rectal swabs examination is criteria fix for patient discharge can be regarded as a caution for COVID-19 nosocomial and community outspread. Nevertheless, hyposmia and hypogeusia are a sign and primary alarm during rapid self-isolation.[40]

Radiological Features of COVID-19

Prior detection and treatment of COVID-19, chest computed tomography (CT) scan, and chest X-ray are the efficient radiological examinations.[41] The radiological findings of COVID-19 pneumonia imitate the feature of influenza and pneumonia associated with SARS-CoV, and MERS-CoV.[42-46]The radiological finding of Wuhan shows that, bilateral pneumonia (75%) expressed by some patients, and remaining (25%) infected patients expressed with unilateral pneumonia. CT scan patients showed increased attenuation in the lung with preserved bronchial and vascular markings in 14% patient.[2] A subsequent study, reported that mainly peripheral abnormality (54%) and they observed right lower lobes infection of affected segments (27%) among 849 patients.[41] The radiological evaluations of COVID-19 pneumonia on chest CT are fluctuating and comprehensive. Serious COVID-19 cases include many grinds-glass opacity (GGO) or hazy opacity lesions with interlobular/intralobular septal thickening, bilateral patchy shadowing, and abnormalities of the interstitium are the common finding of chest CT found in a range of (4-82 %) patient. Rarely reported findings are pulmonary cavity lesion, excess fluid accumulation in the pleural cavity (pleural effusion), and lymphadenopathy.[47-50] Sometime, RT-PCR shown positive results with no alteration in CT for SARS-CoV-2. However, symptomless patients manifesting positive CT detection doubtlessly create challenges towards patients with false-negative RT-PCR outcome.[51]

Diagnostics

Some diagnostic measures for COVID-19 recommends by Centers of Disease Control and Prevention. Specimens/swab mainly collect from upper and lower (oropharyngeal or nasopharyngeal and bronchoalveolar lavage or endotracheal tube) respiratory tract and often specimen collect from the nasal wash, or during aspiration. During pneumonia, RT-PCR examination of the specimens and the often serological tests may also be preferred. Recently, within 3.5-4 hr results are given commercially, obtained from Roche (cobas® SARS-CoV-2) test system which approved by the USFDA. It is an assay for dual-target occupied with fully processed (negative, positive and internal) control to certify accuracy and selectivity (SARS-CoV-2 RNA and E gene fragment are constant in all members of the Sarbecovirus subspecies). On FDA approved another qualitative test system from Cepheid Inc (USA) (Xpert® or Xpress SARS-CoV-2), and it takes 45 minutes to give the result declared on March 21, 2020. Positive results detected on the basis of the presence of over one targeted gene. The present methods of screening believe in the existence of the plentiful genome of viruses at the sample collection site. Several reports showed that top level of IgM antibodies expressed in subclinical and symptomatic patients, following 5 days beginning of the disease. It suggests that ELISA based IgM assay in combination with PCR amplify the sensitivity detection.[52]

Table No. 1. Complication, Laboratory and Radiological feature of COVID-19

System	Symptom	X ray of Chest
Respiratory	• Sore throat • Cough • Strongness of breath • Rhinorrhea	• Patch showing • Multiple GGOS • Septal thickening • Interstitial abnormalities
Gastrointestinal	• Hypogeusia • Hyposmia • Nausea	**Blood test** • Increase C reactive protein • Decrease WBC count • Decrease lymphocytes • Decrease platelet
CNS and Others	• Fever • Fatigue • Headache • Myalgia • Confusion	**Diagnostic** • RT-PCR • IgM ELISA

2. REPURPOSING AND DEVELOPMENT OPPORTUNITIES OF DRUGS AGAINST COVID 19

Pharmacological management

Many countries provide the greatest efforts to execute control master plan and development of proper preventive/proper precautionary measurement. Now existing antiviral drugs or directly acting antiviral drugs and vaccines are not available for the human and animal treatment in CoV induced pneumonia or infections (COVID-19).[53-55] Regrettably, the latest CoV proliferating with contrasting sequence of RNA creates challenge towards drugs and vaccine development against different variants of CoV. Thus

repurposing of antiviral and anti-inflammatory drugs both synthetic and natural source is essential for the management of COVID-19. Several on-going trials are now designed based on repurposing. Likely, several trials were started off to test and develop the specific or promising drug or vaccines candidates and antibodies specifically targeting SARS-CoV-2. Based upon on their target site present therapy may be broadly classified into two groups.

1. Directly acting CoV inhibitors or Viral genomic replication inhibitor - (I) Viral enzyme inhibitors or nsp inhibitors such as inhibitors of 3-chymotrypsin-like protease, inhibitors of RNA-dependent RNA polymerase (RdRp), inhibitors of papain-like protease (II) viral entry inhibitors (towards human cells)
2. Human immune system modulators- (I) Innate response booster; (II) Inflammatory processes (that cause lung injury) inhibitor.

Available therapeutics for management of COVID-19 are mainly based upon earlier experience in the management of SARS CoV and MERS CoV which was done preclinically or clinically. The extensive drugs therapies that can be efficacious in COVID-19 management are remdesivir, lopinavir/ritonavir combination along with interferon-β, convalescent plasma, and monoclonal antibodies (mAbs). However, clinical efficacy, and safety studies, should take into consideration prior to their use in pneumonia patients of COVID-19.

3. REPURPOSING BASED PRECLINICAL AND CLINICAL TRAILS

Viral Protease inhibitor

Ivermectin

FDA approved Ivermectin as an anti-parasitic agent. It also showed its activities against human immunodeficiency virus (HIV) and dengue virus. Viral nuclear protein transportation is crucial for reproduction and development. However, inhibition of nuclear transportation is aworkable approach in therapy toward RNA viruses. Ivermectins inhibit (up to 5,000-fold) SARS-CoV-2 RNA after 48 h of infection has already proven in in-vivo study. Ivermectin's anti-parasitic use has already proved its safety profile. Following to prove its efficacy now Peter Doherty Institute of Infection and Immunity and Melbourne and Monash BDI, Clayton, Victoria start its trials to solve the adequate dosing on the management of COVID-19.[56-59]

Lopinavir/Ritonavir

During replication, cleavage of precursor polypeptides and encoding of aspartyl protease enzyme playing an important part by HIV pol gene. Thus lopinavir and ritonavir combinely inhibit protease of HIV. Lopinavir and ritonavir individually showed their capacity to inhibit the CoV or 3-chymotrypsin- like pro protease (3CL1 protease) and too efficacious against SARS and MERS proved in several *in-vivo* and *in-vitro* investigation.[60-63] Lopinavir/ritonavir combination also expressed little benefit in mild to moderate COVID-19 patients (NCT04252885) observed during the clinical trial.[64] Clinically Lopinavir/Ritonavir application is a time restricting step because they are mainly effective during the early phase of viral replication (initial 7-10 days) but delayed therapy initiation had no effect, move it backward.[63, 65] Clinically lopinavir 400 mg and ritonavir 100 mg combination used a dose of 500 mg twice daily for 14 days used in COVID-19 treatment.[66,67] In another trial, no benefits of lopinavir and ritonavir combination were observed on severe COVID-19 patients (ChiCTR2000029308).[67,68] However, side effects may be worse by combination therapy in patients of COVID-19.

Camostat mesylate

SARSCoV-2 or virus-induced mast cell activation release multiple pro-inflammatory leukotrienes, cytokines (cytokine storm) and chemokines lead to the development of inflammation (bronchoconstriction). Mast cells also contain the serine protease tryptase ACE2, which convert angiotensin I to angiotensin II via an active renin angiotensin system. Thus, Camostat mesylate, an approved agentto treat pancreatitis in Japan and South Korea, prevents entry of nCoV cell in-vitro through inhibition of the host serine protease, (TMPRSS2). This new mode of action provides a supplementary drug target for future research developed mutually by the University of Aarhus, Denmark and German Primate Center-Leibniz Institute for Primate Research, Gottingen and plans for the Phase I/II CamoCO-19 trial (NCT04321096).Cocrystal and Kansas State University Research Foundation mutually develop novel protease inhibitor to treat CoVs. Recently they start its preclinical testing.[69]

RdRp inhibitor

Remdesivir

Remdesivir or GS-5734 is a monophosphate prodrug, after metabolism converted to an active C-adenosine nucleoside triphosphate (structure resemblance to adenosine) and shows a wide range of antiviral activities in case of RNA viruses. In developing viral RNA, it enter and obstruct the action of RdRp and reduce developmental stage of the viral RNA chain and replication of viral genome. Gilead Sciences (USA) originally developed it against the Ebola virus, and for its low EC_{50}/safety and selectivity towards host

polymerase, it showed promising result in National Institute of Allergy and Infectious Diseases and PALM Clinical Trials of Congo, Beni (NCT03719586) during the recent Ebola outbreak.[70] However, *in-vitro* results of remdesivir exhibit antiviral activities against SARS-CoV (SARS-CoV-2) with EC_{50} 0.77 μM and EC_{90} of 1.76 μM, respectively, and in murine lung infection models with MERS-CoV, it prevented lung hemorrhage.[71-73] Single and multiple dose intravenous infusion showed linear pharmacokinetics with a long half - life of greater than 35 h in between 3-225 mg and well tolerated with no proof of liver or kidney toxicity in phase I clinical trials. However, administrations of multiple-dose, increase reversible aspartate aminotransferase and alanine transaminase. The latest loading dose under study is a single 200-mg, followed by a daily infusion of 100 mg. Previously it was reported that on the 7th day of hospitalization remdesivir was applied on first COVID-19 patient in the USA and its condition improved on the 8th day with no noticeable adverse effect.[74] Multiple trials and phase III randomized control trials (RCT) are conducted in different countries including china (NCT04292899, NCT04292730, NCT04280705 and NCT04252664, NCT04257656), expected to be over in May 2020.[68] Primarily, remdesivir is not FDA-approved drug but recently Japan ratifies application of remdesivir on COVID-19 patient.

Favipiravir

Favipiravir (T-705), is a prodrug of a purine nucleotide (favipiravir ribofuranosyl-5′-triphosphate), its structure resembles with endogenous guanine, flu drug originally started by Fujifilm Toyama Chemical, Japan under the brand name Avigan. Fujifilm has started phase III trial of this drug and also enhanced its manufacturing. It is an approved drug for influenza treatment. Through competitive inhibition it inhibits RNA-dependent RNA polymerase and halt viral replication.[75] *In-vitro* study (Vero E6 cells) revealed its low EC_{50} (61.88 μM/L) against SARS CoV-2.[72] Previously, randomized, multicenter trial of favipiravir was conducted and differences in clinical recovery at day 7 were observed as compared to Arbidol/Umifenovir (n = 120) to treat moderate (71.4 % favipiravir and 55.9 % Arbidol, P = .019) and severe (No significant differences were observed) COVID-19 infections.[76]Recently Glenmark Pharmaceuticals received approval from India's drug regulator (DCGI) on antiviral tablet Favipiravir in late April and has commenced Phase-III trials in India. Another Indian manufacturer, Strides pharma so far go ahead sending the favipiravir to gulf region territories.

Ribavirin

Ribavirin, an analog of guanine, inhibits viral RNA-dependent RNA polymerase. Combination therapy and high concentrations (1.2-2.4 g orally every 8 h) required to inhibit viral replication, at this higher dose Ribavirin produce hematologic (hemolytic anemia in than over 60 % of patients) and liver toxicity (elevated transaminase in 75% of patients) limits its use.[77] Clinically Ribavirin in combination with lopinavir/ritonavir and interferons-β1b (NCT0427668 in Hongkong) and again Ribavirin in combination with interferon-α1b (ChiCTR2000029387 in China) showed no noticeable effect but toxicity was appeared (requir blood transfusions in 40% of patients) in the treatment of MERS.[78] Primarily, Ribavirin is a teratogen and contraindicated in pregnancy. The inconclusive efficacy data with ribavirin for other nCoVs and its toxicity narrate that it has limited merit for treatment of COVID-19.[79]

Virus–Cell Membrane Fusion Inhibitor

Hydroxychloroquine and Chloroquine

Hydroxychloroquine and Chloroquine are well-known for treatment of malaria and systemic lupus erythematous (SLE) and rheumatoid arthritis like persistent inflammatory diseases (RA). Hydroxychloroquine and Chloroquine inhibit fusion, a process of cell membrane because of which virus entry into the host cells, required glycosylation of ACE2 cellular receptor, rising neutralizing pH of endosome.[80] These agents also have a capacity for reduction of cytokine production and inhibition of autophagy and lysosomal activity in host cells, act as immunomodulatory agent.[81,82] Hydroxychloroquine and chloroquine with EC_{50} 6.14 and 23.90 μM in *in-vitro* showed inhibition of SARS-CoV-2, 24 h after the incubation.[83] Recent information from china revealed that chloroquine was successfully used to treat over 100 COVID-19 cases due to increased viral clearance, decreased disease progression and improved radiological findings.[84] Likely, many randomized trials speedily conducted in China, specify productivity of hydroxychloroquine for COVID-19-associated pneumonia. However, validations of these claims are needed in near future. Similarly, A recent open-label nonrandomized clinical trial from France (n = 36, 20 in the hydroxychloroquine group and 16 in the control group) revealed that hydroxychloroquine (200 mg, by mouth every 8 hours) improved virologic clearance (Day 6, nasopharyngeal swabs in hydroxychloroquine = 70% (14/20) vs nasopharyngeal swabs in control 12.5% (2/16), P = .001). Similarly, azithromycin and hydroxychloroquine combination was trialed against hydroxychloroquine monotherapy showed superior viral clearance (Combination = 6/6, 100% vs hydroxychloroquine alone = 8/14, 57%).[85] Small sample size (n=20 and only 6 receiving hydroxychloroquine and azithromycin), additive cardiotoxicity with combination therapy do not approve this regimen without additional studies. Another randomized trial was conducted in China (n=30, for 5 days) showed the effect of hydroxychloroquine

with standard care (supportive care, interferon, and other antivirals) and hydroxychloroquine alone on viral clearance (on day 7, 86.7% vs 93.3%, P>.05) respectively.[86] However, a physiologically based pharmacokinetic modeling (PBPK) study suggested best dosing regimen for hydroxychloroquine and chloroquine in COVID-19 treatment start withan oral dose of 500 mg (once or twice daily) and then it progressively reduce to 400 mg for 1 day accompanied by 200 mg (twice daily) respectively. Further studies are needed to delineate the optimal dose for COVID-19.[84]

Latest clinical study from France manifest Hydroxychloroquine and azithromycin combination treatment canprovide positive effect in serious COVID-19 patient.[85,86] However, hydroxychloroquine can develop significant adverse events (<10%), including prolongation of QT interval in ECG (prolongation of ventricular action potential duration), hypoglycaemia, neuropsychiatric effects, and retinopathy.[87,88] In combination with Hydroxychloroquine azithromycin prolong QT interval. It is advisable that before initiation of these medications baseline electrocardiography (ECG) were taken to evaluate prolongation of QT interval because of the potential for arrhythmias, preferably in critically ill patients and those taking concomitant azithromycin and quinolones (QT-interval prolonging medications).[89] Hydroxychloroquine and chloroquine use is considered safe in pregnancy.[90] Future studies are needed to set out the favourable dose in COVID-19.

Umifenovir

Umifenovir (also called Arbidol hydrochloride or Arbidol) is an antiviral drug use in COV through repurposing. It develops by Pharmstandard, Russia with a unique mechanism of action targeting the S protein/ACE2 interaction and inhibiting fusion of membrane in the viral envelope. Briefly, it prevents fusion of the viral membrane (hemagglutinin, a major glycoprotein) with the endosome after endocytosis. Recently, its promising candidature is accepted in China and Russia for prophylaxis and treatment of influenza.[91] However, based on *in-vitro* data against SARS this drug is a candidate of interest for treating COVID-19 with a current influenza oral dose (200 mg in every 8 h) (NCT04260594, NCT04255017).[92] Limited clinical outcome showed with Umifenovir in China for COVID-19. Anon-randomized clinical study (n=67) of COVID-19 showed that Umifenovir 9 days therapy associated with lower mortality rates (0/36) and higher discharge rates (5/31) compared with patients not receiving this drug.[93] This provisional data not validate the advantage of Umifenovir for COVID-19, but ongoing RCTs in China validating this agent.

Recombinant Human Angiotensin-converting Enzyme 2

Recombinant human Angiotensin-converting Enzyme 2 (rhACE2) is soluble APN01), may inhibit the entry of SARS-CoV-2 through inhibition of viral S protein from cellular interaction with the ACE2. In in-vitro rhACE2 impede replication of SARS-CoV-2 (1,000-5,000 times) in cell and organoids (embryonic stem cell), described in a recent study.[94] It is believed that serum angiotensin II level can decrease by the administration of rhACE2 by aside the substrate from the ACE, block additional ACE2 receptor activation and that prevent enhancement of pulmonary vascular permeability and ultimately prevent acute respiratory distress syndrome (ARDS). Further Apeiron Biologics commenced a dose-upswing, placebo controlled, double blinded trail on intravenous rhACE2 (APN01B) to access its safety and acceptability. Recently small pilot study (NCT04287686) is ongoing in China, to find out the role of rhACE2 in COVID-19 pneumonia and ARDS. [95]

I. Theoretical conflict or contrasting effect of ACE inhibitors

Host cellular receptor ACE2, used by SARS-CoV-2 for its entry. This mechanism has energizing discussions on ACE inhibitors and/or angiotensin receptor blockers, whether they might treat COVID-19 or vice versa. Conflicting theoretical data available to determine whether these agents have a harmful or protective effect on patients with COVID-19. Theoretically, these drugs upregulate ACE2 receptors, which may worsen outcomes if it increases viral entry. Contrary to this, theoretically angiotensin receptor blockers may provide clinical benefit because of inhibition of ACE2 receptors. Further research, clinical trials and practice guidelines are required to test their efficacy in COVID-19. Dry, interminable cough is a major drawback associated with angiotensin converting enzyme inhibitors (ACEI) administration showed by some researcher. This drawback may attenuate by natural product noscapine for its antitussive effect.[96]

Innate Immune System enhancer

Natural Killer Cells

Boosting of innate immune responses always essential for weakening of the immune system with an increase of age. Innate immune system comprise of Natural killer (NK) cells that secures fast reaction to infection associated with virus. Macrophages and NK cells pulmonary migration perform SARS-CoV clearance mentioned in some previous report. The innate reaction prevents SARS-CoV infection for its self-capability to enhance the production of cytokines andchemokine with no help from the CD8+ T cells and

antibodies. In continuation of effort phase I trial (NCT04280224) undergoing in China, to determine inclusion of NK cells may assist for clearance of virus in pneumonia of COVID-19, completed by the end of 2020. [97]

Henceforward, Green Cross Lab Cell (South Korea) and Kleo Pharmaceuticals (U.S.) mutual collaboration focus on repurposing of their NK based anti-cancer commodities to manage COVID-19. Recently, NK cells got from hematopoietic stem cell of Placenta has already developed by a USA-based company Celularity and coded as (CYNK-001).

Other cells

Cardiac cell therapy originally developed by Capricor Therapeutics, Inc comprising allogeneic cardiosphere-derived cells named CAP-1002. The cells release exosome that taken up by T cells and macrophages and restore cell through its preventive capacity. Previous preclinical data showed that this candidate prevent activation of macrophage and inhibit release of pro-inflammatory cytokines in inflammation with sepsis and autoimmune diseases. Capricor Therapeutics files IND application to the FDA, to investigate this in patients of COVID-19. [98]

Recombinant Interferon

Virus-infected cells secret type I interferons, showed a wide range antiviral action against respiratory syncytial virus (RSV), hepatitis C virus (HCV) and SARS-CoV and further, interferon β showed its antiviral capability against MERS-CoV, used alone or in combination with additional drugs.[99, 100] IFN-alpha2b candidate recently developed by Tianjin Sinobloway Biology Trials are now ongoing to investigate their efficacy and safety in COVID-19 pneumonia (NCT04293887).

Adenovirus and Rabis virus has a viral vector to show S protein of MERS-CoV. Recombinant adenovirus (RAV) and recombinant rabies virus (RV), based vaccine showing S protein of MERS-CoV prompts intrinsic lung resident memory T-cell, secretory IgA and IgG response. Intranasal administration of RAV and RV based vaccine to BALB/c mice provide counterbalancing long-live cellular immunity and prompt antibody reaction, encouraging its defence in opposition to MERSCoV.[101]

Reducing the Inflammatory Response

Fingolimod

Oral immunomodulating agent Fingolimod structurally resemble to lipid sphingosine-1-phosphate (S1P) that primarily used for treatment of refractory multiple sclerosis. It, act as potent and competitive S1P1 receptors antagonist in lymph node T cells of. Uncontrolled immunopathogenesis may decrease by reduction of T lymphocytes associated with pulmonary influx is another approach for fingolimod. Nowits phase II trails are ended on July 2020 in First Affiliated Hospital of Fujian Medical University (NCT04280588) (n=30).[102] They exclusively measure the change of pneumonia severity on X-ray images (0.5 mg OD orally, for three consecutive days).

Thalidomide

Thalidomide can inhibit synthesis of proinflammatory cytokine TNF-alpha. Thalidomide has potentially repurposed to prevent angiogenesis, inflammation, and fibrosis. Thalidomide mainly used in therapy of inflammatory Crohn syndrome and Behcet's syndrome.[103] Further, several animal studies showed its advantage in mice infected with H1N1 virus for inhibition of cytokine fabrication and inflammatory cells infiltration.[104] Recent researches (NCT04273529, NCT04273581) centre of attention is on immunomodulating outcome of thalidomide that might turn down injury of lung cause for SARS-CoV-2 unrestricted immune reaction.

Corticosteroids

The logic to use corticosteroids is to reduce the host inflammation associated lung injury and ARDS. However, this interest may be hindered by adverse effects, including delayed viral clearance from the respiratory tract and blood and risk of secondary infection.[105] Other major complication including hyperglycemia, psychosis, and a vascular necrosis are observed due to corticosteroids application.[77, 106] A recent observational study of methylprednisolone for COVID-19 in China compare risk of death between methyl prednisolone user (46 %, (23/50)) vs non user (62 %, (21/34)) with ARDS. Therefore, the adverse event and lack of proven benefit for corticosteroids put backward their routine use in patients with COVID-19. However, research has already started (NCT04273321, NCT04263402) to investigate their benefit and welfare. [107]

Mesenchymal Stem Cells

Mesenchymal stem cell (MSCs) can impede pro-inflammatory cytokines and develop paracrine aspects need for repairing of tissues. *In-vivo* and *in-vitro* (avian influenza viruses) experimental report suggest their capacity to inhibit inflammatory infiltrate and reinstate endothelial permeability due to its immunomodulatory effect.[108] Now, umbilical cord and dental pulp are the source of MSCs, under trail (NCT04293692, NCT04269525, NCT04288102, NCT04302519) to explain their role in COVID-19 pneumonia.[109]

Cyanta Therapeutics, develop MSCs based treatments based on its useful preclinical facts in lung disease and sepsis hopeful for its application against COVID-19. Recently these MSCs intravenous transplantation was prove to be effective and safe in COVID-19 pneumonia patients (n = 7) of Beijing, China. MSC transplantation quickly (2 days) improve pulmonary function and symptom of all patients and while three severe pneumonia patients after 10days recovered and discharged.[110]

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) shows various physiological effects on the immune system based upon dose dependency. IVIG in low doses capable to restore antibody deficiencies (0.2-0.5g/kg) and in a very high dose (2g/kg) it inhibits phagocytosis and proliferation inflammatory cells and obstruct cytotoxicity associated with antibody, for its immunomodulatory functions.[111] Phase II trial has already started (NCT04261426) based on the complementary effects of IVIG at a low dose (0.5g/kg for 5 days) in pneumonia of COVID-19.

SARS-CoV-2-Specific Neutralizing Antibodies or Universal CoV vaccine

Viral infections halted by antibodies mediated humoral immune response. Thus, neutralizing antibodies targeted specific surface epitope development is another perspective to treat COVID-19.[112] Eli Lilly, USA and AbCellera, Canada collaboratively develops an antibody to counter patient's infection associated with SARS-CoV-2. They isolated immune cells (5 million) from first phase recovered COVID-19 patient of U.S. and also point out latent anti-SARS-CoV-2 antibody sequences (greater than 500), to get the effective ones. However, they successfully develop the functional antibodies with specificity in case of the West Nile virus.[113] Although this approach is a time-consuming but several companies like Vir Biotechnology, Inc. (California), Immuno Precise (Canada), Mount Sinai Health System (New York city) and Harbour BioMed (China) put their best effort to tackle SARS-CoV-2 through application of monoclonal antibodies but all of them are under preclinical stages.

COV proteins, restoring of T cell mediated preventive responses and suppress virus. Neutralising protein induce cytolytic feedback of T cell in COVID-19. These responses inhibit S protein of virus and help to resolve infection in the host.[114]

Man-made protein monoclonal Antibody for passive immunization

Monoclonal antibodies adjunctive therapies for COVID-19 administered against inflammatory cytokines and development of innate immunity.

1. Anti-C5a Monoclonal Antibody

Complement activation (C5a bioactive molecule) takes place during acute lung injury that split from C5, responsible for the tissue injury development. C5a possess a crucial role in recruitment, and enhancement of vascular permeability pulmonary system which recruit T-lymphocytes and neutrophils. It showed that lung injury could reduce by anti-C5a therapy because of its capacity to attenuate, leakage of vascular bed and influx of neutrophil into the space of alveoli. Thus, anti-C5a monoclonal antibodies (BDB-1, IFX-1 or InflaRx), launched and, produced (Beijing Defengrei Biotechnology Co., Beijing Staidson Biopharma) targeting the physiology of inflammatory reaction that may decrease the injury of lung caused by SARS-CoV 2.[115]

2. Cytokines inhibiting monoclonal antibody

Several pro-inflammatory cytokines such as interleukins (IL-1, IL-6) and tumor necrotic factor (TNF- α), are mediator of inflammation present in the human body.[116] The enhanced concentration of IL-6 make an interplay in mechanical ventilation.[117] Neutrophils, monocytes and macrophages are expressed on IL-6 membrane-bound receptors (mIL-6R, CD126), responsible for inflammatory signaling. Faster reduction of lung elasticity and bronchoalveolar acute inflammation cause for increased IL-6 level. Hence, IL-6 specific inhibition is a promising tool for attenuation of inflammation associated damage.[118]

IL-6 inhibitors prevent, enhanced immune response associated with lungs and other organs damage and release of cytokine (cytokine storm).[119,120] Earlier Chinese case series narrates IL-6 responsibility for dysregulated inflammation.[121] Thus, monoclonal antibodies against IL-6 may diminish this process and improve clinical outcomes.

I. Tocilizumab

Tocilizumab approved by FDA, a monoclonal antibody act as IL-6 receptor antagonist. It follows chimeric antigen receptor T-cell therapy and use for RA treatment and cytokine release syndrome. Previous report showed that Tocilizumab at a 400mg dose improved respiratory function (91%) and increase rate of patients (n=21) discharge in COVID-19 but this study were conducted with absence of a comparator group which limits the explanation of drug specificity.[122] Several randomized trials of tocilizumab, alone or in combination with favipiravir conducted by Chugai Pharmaceutical and Zhejiang Hisun Pharmaceutical in COVID-19 patients with severe pneumonia, are ongoing in China (NCT04310228, ChiCTR200002976).[123]

II. Sarilumab

Sarilumab with brand name Kevzara is an IL-6 receptor antagonist already approved in treatment of RA is being investigated in a multicenter, double-blind, phase II or III trial conducted by Regeneron Pharmaceuticals and Sanofi in severe hospitalized COVID-19 patients (NCT04315298). However, its effcacy in treatment of SARS-CoV-2 is still unknown.[124]

III. Bevacizumab

Vascular endothelial growth factor (VEGF) is a mediator that can prompt injury of endothelium and enhance microvascular permeability. Bevacizumab is known as a recombinant humanized monoclonal antibody with anti–VEGF specificity, capable to inhibit angiogenesis, extensively used in multiple types of cancers treatment. Now, a trial (NCT04275414) is carried out to assess the Bevacizumab efficacy in infection associated with SARS-CoV-2.[125]

IV. Siltuximab

EUSA Pharma (Europe) has started his investigation to assess the Siltuximab efficacy, an anti-IL-6 monocloncal antibody for treatment of ARDS in COVID-19 patients.[127]

V. Others monoclonal andpolyclonal antibody

Recently Tiziana Life Sciences (UK) developed anti-IL-6 receptor antibody (TZLS-501) for a reduction in circulating IL-6 levels to treat the COVID-19 associated ARDS. [127]

Eculizumab (soliris) (antibody; NCT04288713) is another monoclonal antibody inhibiting terminal complement of cytokine axis and its clinical trials are ongoing in China and its expanded phase II trial by Alexion Pharmaceuticals, USA.[68]

Namilumab a whole human monoclonal antibody inhibits expression of GM-CSF, developed by Izana Bioscience, England. A small trail shows its application in treatment of COVID-19 patients before ICU admission and prior to ventilation or those are in worse condition. Its Phase III trial may start in case of an emergency.[128]

Recently Celltrion Healthcare and KCDC (Korea Centers for Disease Control and prevention) mutually screen monoclonal antibodies to find the lead ones that neutralize SARS-CoV-2.

Emergent Biosolution, Maryland develops Human and Equine-derived, polyclonal hyperimmune with antibodies (COVID HIG and EIG) derived from plasma for treatment of SARS-CoV-2. It uses in severe hospitalized patients and provide immediate protection from infection. Its clinical studies are ongoing.

Human polyclonal antibodies that delivered by high-potency immunotherapy are developed by CSL behering, USA and SAB Biotherpeutics, US against SARS-CoV-2. Its testing will start soon.[127]

Table No. 2. A list of therapies and vaccines development for COVID-19

Company	Therapeutics under Trail	Vaccine under development
Gilead Sciences	Remdesivir (GS-5734)	NA
Biocryst Pharma	Galidesivir	NA
US FDA	Chloroquine	NA
Toyama Chemical	Favilavir	NA
Innovation Pharmaceuticals	Brilacidin	NA
APEIRON Biologics and University of British Columbia	APN01	NA
Roche	Actemra	NA
Regeneron	Kevzara	NA

CytoDyn	leronlimab	NA
OyaGen	OYA1	NA
Synairgen Research	SNG001	NA
Lattice Biologics	AmnioBoost	NA
Algernon Pharmaceuticals	Ifenprodil	NA
Airway Therapeutics	AT-100	NA
Cipla	LOPIMUNE	NA
Janssen Pharmaceutical	PREZCOBIX®(darunavir/cobicistat)	NA
Vir Biotechnology	Monoclonal antibodies	NA
NanoViricides	Nanoviricide® technology	NA
Takeda Pharmaceutical Company	Hyperimmune globulin (H-IG) therapy	NA
CEL-SCI	Ligand Epitope Antigen Presentation System (LEAPS) peptide immunotherapy	NA
Emergent BioSolutions	Plasma-derived product candidates	NA
Pfizer	Novel compounds for Therapy	COVID-19 vaccine
Serum Institute of India	NA	COVID-19 vaccine
Inovio Pharma	NA	INO-4700 (DNA vaccine)
Clover Biopharmaceuticals	NA	Recombinant subunit vaccine (Protein based Trimer vaccine)
Moderna and Vaccine Research Center	NA	mRNA-1273 vaccine
University of Oxford	NA	ChAdOx1 nCoV-19 (Adenovirus Vector)
Inovio Pharmaceuticals and Beijing Advaccine Biotechnology	NA	INO-4800 (DNA vaccine)
Medicago	NA	VLP Coronavirus vaccine
Altimmune	NA	AdCOVID (Intranasal Nasovax platform)
Novavax	NA	NVX-CoV2373Protein based vaccine
Tonix Pharmaceuticals	NA	TNX-1800live modified horsepox vaccine
Entos Pharmaceuticals	NA	Fusogenix DNA vaccine
MIGAL Research Institute	NA	Avian Coronavirus Infectious Bronchitis Virus (IBV) vaccine (Protein expression vector)
Hong Kong University of Science and Technology	NA	B-cell and T-cell epitopes for Vaccine development
Zydus Cadila	NA	DNA vaccine/ recombinant measles virus vector -based vaccine
AJ Vaccines		Develop antigens that mimic the native structures of the virus

Symptomatic Control

1. Pathogen Specific Artificial Antigen- Presenting Cells or T cell immunotherapies

These are T cell therapy specifically uses in viral infection to restore natural T cell immunity. Physiologically, cancer cells and viral infections can suppress by antigen specific T cells. Thus,enormous amount of time dependent T cells and antigen specific T cells are essential to develop that start invasion of SARS-CoV-2. Immense quantities of T cells produce by transformation and proliferation of analogous effector, antigen specific cytotoxic T cells, and effector T cells activating antigen-presenting cells (aAPCs). Hence, lenti virus vector able to deliver the genetically changed aAPCs, expected to induce the T cells native to human, and that leads to ultimate proliferation and differentiation. Recently, Trials are conducting on aAPCs and its combination with cytotoxic T cells (having specificity towards antigen) to test their immunogenicity and safety issue (NCT04299724, NCT04276896). Recently, joint venture of ALLO Vir, US and Bayer College of medicine, US development T cell immunotherapies candidate, ALVR106 against influenza virus, parainfuenza virus, respiratory syncytial virus and human metapneumo virus. Now they plan to apply this agent against SARS-CoV-2. Kentucky Bio Processing (KBP) has developed a potential COVID-19 vaccine made up of COVID-19's genetic sequence cloned portion that leads to development of potential antigen under preclinical stage. It carried antigen reproduction inside the Tobacco plants and it purified further antigen after collection.[51]

2. Immunoglobulin or Convalescent plasma Therapy

COVID-19 potential therapy, convalescent plasma or hyperimmune immunoglobulins,[129] logic behind this treatment is that recovered patients antibodies can help infected cell viral clearance and immune clearance. They have reported several unreliable reports for convalescent plasma as rescue therapy in SARS and MERS.[130,131] An observational trail of convalescent plasma in H1N1 influenza critically ill patients was conducted in 2009 and comparison were made in reduction of mortality between convalescent plasma receiving group (n=20) and nonreceiving group (20% vs 54.8%, P = .01).[132] Theoretically, this therapy primarily provides benefits within the first 7 to 10 days of infection, when virus highly present in blood so primary immune response not developed.[133] Several reports describing preclinical development of a humanized monoclonal antibody against a common epitope to inhibit infection associated with SARS-CoV and SARS-COV-2. Although current commercial immunoglobulin preparations likely lack protective antibodies to SARS-CoV-2. A case series of COVID-19 in Wuhan, China, treated 3 patients with intravenous immunoglobulin at a dose of 0.3-0.5 g/kg/d for 5 days was recently published. [134] On March 24, 2020, Grifols, Spain, in collaboration with the BARDA (Biomedical Advanced Research Development Authority), apply for emergency INDA (investigational new drug application) and screening donors for COVID-19 convalescent plasma or hyperimmune globulin therapy.[135] Johns Hopkins lab also starts study of antibodies obtained from plasma or serum of COVID-19 recovered people.[136]

3. Vaccine

The most effective long-term strategy to prevent future outbreaks of this virus would be the development of a vaccine providing protective immunity. Genetic vaccines are easier for purification and lower costs of production as compared to conventional vaccines. Nucleic acids structure of are simple to prevent incorrect folding risk, occur in recombinant protein-based vaccines. However, key factors that impact the genetic vaccines immunogenicity are appropriate time intervals, amount of plasmid transport and administration route. We have suggested several vaccines based upon nucleic acid based on the coding sequence of S protein of SARS-CoV-2 genome.[137] However, a minimum of 12 to 18 months would be required before widespread vaccine deployment.

I. Stabilized Subunit Vaccines

Fusion needs viral glycoprotein conformational change from pre to post form. Glycoproteins are relatively unstable during pre-fusion but produce strong immune responses. Molecular clamp technology based stabilized subunit vaccine developed by a mutual collaboration of GlaxoSmithKline (GSK), CEPI and the University of Queensland, that's permit stable recombinant viral proteins in their pre-fusion form. It was also reported that molecular clamp technology based vaccines already showed their capacity in influenza virus and Ebola virus for neutralizing antibodies production and to be potent at 37^0C after two weeks.[138]

II. mRNA-1273

Synthetic strand of mRNA (Moderna's mRNA-1273) stabilizes viral spike protein perfusion. Thus, after IM injection, it is anticipated to elicit spike protein specific antiviral response towards SARS-CoV-2 in human bodies. It is comparatively safe than other vaccine made from inactivated pathogen and ready to be tested.[139]

Self-amplifying RNA vaccine, developed by Imperial College, London within 14 days after getting the viral sequence obtained from China. It designed to inject into a muscle where it develops a new genetic code and proteins resemble to the surface of

coronavirus and express a protective immune response. The preclinical research on the animal already complete from February 10 and now plans to start clinical trials in June or July.[140]

Two strategies employed by mRNA vaccine, production of virus-like particles (VLPs) having replica of native COVID-19 viruses and production activate immune responses after insertion in the host. In another approach mRNA are uses to express spike protein RBD of COVID-19 that induce neutralizing-antibodies in the human body. This multiple approach was applied by Fudan University, Shanghai, JiaoTong University, China and RNACure Biopharma, USA with a mixture of three genes of COVID-19 mRNA and it initiate VLPs production in co-transfect human cells. Similar vaccine developed by Medicago, Canada from the gene of SARS-CoV-2 that creates VLP. It now conducts safety and efficacy study of this vaccine on *in-vitro* and *in-vivo*. Further, its trials on human will be started in July/August, 2020.[141]

Intranasal single mRNA-T cell epitopes based vaccine adjuvant developed and repurposed by a mutual collaboration of Epivax, USA; REPROCELL, USA;CEV lab, Italy which trigger CD4 and CD8 T cell expression activated by dendritic cells. It applies these vaccines through a nasal atomizer targeted towards nasal mucosa.

Neurimmune, Switzerland and Ethris, Germany plan to develop a mRNA-based antibody taken through the inhaler and ultimately it enters the lungs of COVID-19 patients. Its clinical trial will start very soon.

Ii-Key or MHC class II epitope hybrid antigenic peptides are 100 times more powerful than individual peptides in immunity development. It is actually a hybrid platform for HIV. Now this platform will apply for Ii-Key-SARS-2 peptide developed by Generex Biotechnology (NuGenerex Immuno-Oncology) and EpiVax. Now it applies for licensing in unfamiliar countries.[139]

III. ChAdOx1 nCoV-19 vaccine

Greffex, US and University of Oxford developed this vaccine, based on S protein genetic sequence of SARS-CoV-2 with a non-replicating helper virus-independent adenovirus vector, now entered phase I/II trial (NCT04324606). It applied through an adenovirus vector which is non-replicating in nature. ACE-2 receptor chiefly expresses in the respiratory and gastrointestinal epithelium and these two main sites cover by adenovirus based vectors of SARS-CoV-2. The probability of dominant immunogenicity always preferred vector genes instead of transgenes.[142]

IV. INO-4800

DNA vaccine INO-4800 developed by Inovio Pharmaceuticals, Pennsylvania and also by ImmunoPrecise Antibodies (IPA), Canada and EVQLV, New York. It comprises encoded sequences of DNA that provide antibodies against SARS-CoV-2. After delivery to human cells, it converted into proteins that produce immune responses.[143, 144]

V. Nanoparticle-Based Vaccines

Viruses belongs to nanoscale objects therefore nanoparticles and viruses operate at the same length scale. This makes nanotechnology approaches powerful. In this technology nano fibre or nano material are applied in immunoengineering for vaccine development. Another approach to incorporate antigens is a nanoparticle-based vaccine. Through covalent bonding or encapsulation nanoparticles and epitopes of antigen form a conjugate that imitate the viruses and helpful for production and proliferation of cytokine and lymphocyte that have specificity towards antigen. Fully humanized antibodies or humanized-nanobodies can cross host cells membrane (Tran's bodies) that infected for virus and also bind to replicating proteins of virus and ultimately inhibit replication of virus. This technology applied for development of heavy-chain antibodies, variable nanobodies or single-domain antibodies (HCAbs, VH/VHHs or sdAbs) and human single-chain antibodies (Hu-scFvs) by Ablynx biopharmaceutical, Belgium. Furthermore, oral or intranasal spray mucosal vaccination not only stimulates mucosal surface immune response but also evokes systemic responses.[145, 146] Thus, nanoparticle vaccines act as a safeguard for humans in case of respiratory viruses associated symptoms. In near future Nucleic acid based nano vaccine, Subunit nano vaccine, Peptide based nano vaccine will come into market having good stability, safety, and scalability.[147] Emergent BioSolutions, Washington and Novavax, Inc use antigen to isolate S protein of CoV and develop a nanoparticle vaccine, expected to provide Preliminary immunogenicity and safety results expected in July 2020. Previously this protein showed its baculovirus system stability.

VI. Other vaccine

AdCOVID is a Single-dose intranasal vaccine help to provide systemic immunity. It originally developed by a joint venture of Altimmune Inc with the University of Alabama at Birmingham (UAB) based on previous influenza platform NasoVAX™ that showed positive immunogenicityresults.[148]

Bayer College of Medicine develops a vaccine that based on recombinant protein with a receptor binding domain (RBD) of spike protein of the COV able to bind receptor present in lung tissue of host.[149]

CoVs S-trimer protein in combination with toll-like receptor 9 (TLR9) agonist vaccine candidate developed by a joint collaboration of Clover Biopharmaceutical and Dynavax Technologies.[150]

Hoth and Voltron Therapeutics (HaloVax), USA sign an agreement with Vaccine and Immunotherapy Center (VIC) of Massachusetts General Hospital and develop Self-Assembling Vaccine (SAV) that prevent infection in COVID-19 patients. Within the next few days this vaccine *in-vivo* testing will start. HaloVax with support from the USA Department of Defense (DOD) previously proved its utility in Lassa fever.[151]

The vaccine that expresses Drosophila S2 insect cell to produce 2019-nCoV viral antigens system, and capsid virus-like particle (cVLP) are applied by ExpreS^{2}ion Biotechnologies and AdaptVac to develop vaccine antigens and test this in *in-vitro* and *in-vivo* in near future.[152]

Miscellaneous Agents

Oseltamivir

Oseltamivir approved to treat influenza, a neuraminidase inhibitor, has no documented *in-vitro* activity against SARSCoV- 2. Initially, in China the COVID-19 outbreak happened during peak influenza season so a large proportion of patients received treatment of oseltamivir in combination with other drugs until SARS-CoV-2 discovery of as the cause of COVID-19.[35] Several clinical trials are ongoing on oseltamivir, but not as a proposed therapeutic medication.[68]

Darunavir

Limited clinical outcome with darunavir has been described in China for COVID-19.[153]Randomized clinical trial (RCT) of darunavir/ cobicistat in China is underway.[68]

Brilacidin

It develops by Innovation Pharmaceuticals Inc in the treatment of head and neck cancer. Previous publish report suggests its inhibitory potential against Vero cells SARS-CoV-2 and it also inhibits pro-inflammatory chemokine and cytokines (IL-6). Brilacidin may act as an important candidate for the treatment of patients in COVID-19. U.S.-based virology laboratory now tests brilacidin for its antiviral efficacy.[154]

Giapreza

Giapreza, a vasoconstrictor drug, developed by La Jolla Pharmaceutical, US. Further, this drug was again approved by the European Commission in August 2019 for adults refractory hypotension with septic shock. Adult patients with septic or other distributive shock may use Giapreza to enhance their blood pressure, but till now it is not available commercially in Europe. Probably, in the near future, it may use in an elderly patient of COVID-19 to prevent shock associated hypotension.[155]

Ibudilast

Ibudilast (MN-166) is an orally bioavailable drug developed by MediciNova, USA. It inhibits macrophage migration inhibitory factor (MIF) and also inhibits phosphodiesterase (PDE 4 and 10). Now the clinical trial of Ibudilast has started by a collaborative effort of Yale's Advanced Therapies Group and MediciNova for COVID-19 associated acute respiratory distress syndrome (ARDS).[68]

Nitazoxanide

Nitazoxanide with its safety profile has broad antiviral activity, but traditionally it used as an anthelmintic agent. It demonstrated its antiviral activity against MERS (inhibiting viral N protein) and SARS-CoV-2 (inhibiting viral S protein) in in-vitro. Nitazoxanide antiviral activity, safety data and immunomodulatory effect authorize its further study as used in SARS-CoV-2 therapy.[156]

Interferon

Interferon-β showed its activity against MERS. Most published studies reported combination therapy of Interferon-β with ribavirin and/or lopinavir/ ritonavir. Similar to others, delayed treatment may limit their effectiveness.[157] Rebif® (interferon β-1a) originally developed by Merck KGaA, Germany and approved by FDA for treatment of multiple sclerosis. The latest guidelines of China register interferons as an alternative for combination therapy.[158] Now it successfully tested in COVID-19 patient of Britain.

Others

Immunomodulatory agent for noninfectious disease showed their *in-vitro* activity and supported mechanism for inhibition of SARS-CoV-2.[53-57]. However, no *in-vivo* or clinical data exist to approve their use for COVID-19.

Apilimod

Apilimod also called LAM-002. It originally developed by Al Therapeutics, USA for treatment of B-cell associated frontotemporal dementia and non-Hodgkin lymphoma. A recent report suggests that it prevents entry of SARS-CoV-2 when using alone and more effective in combination with remdesivir in *in-vitro*. Recently its IND report submitted to FDA being a hopeful drug.[159]

Rintatolimod

Rintatolimod also called Ampligen® originally developed by AIM Immunotech having immuno modulating capacity. Argentina has approved this drug for the treatment of severe chronic fatigue syndrome. Recently clinical trial is ongoing in Netherland for treatment of pancreatic cancer patients. In collaboration with Shenzhen Smoore Technology Research, AIM Immunotech start its research in China to know efficacy of Ampligen® with smoores vaping devices for inhalation of drug deep into lungs in ARDS of COVID-19.[68]

ENU200

Another repurposed oral antiviral ENU200 by Ennaid Therapeutics, GA previously approved by FDA, may block S glycoprotein and Mpro of SARS-CoV-2 and delivers specific antiviral activity. Its Phase III trial will start soon.[160]

Indomethacin

Previous literature indicates, several DNA and RNA viruses including SARS-CoV replication halt by indomethacin. Deal with pathogenesis and replication in many viral infections Cyclooxygenases (COXs) enzyme possesses a crucial role.[161]Indomethacin act as a COX inhibitor (Cyclopentone) having potent anti-inflammatory and analgesic properties.[162,163]

Development of Therapeutics from a natural source

To date, the potential antiviral activity shown by several herbal medicines or their constituents. Some extracts or natural products inhibit viral replication and prove their antiviral property. Apart from plant-derived compounds, several reports also mentioned about marine natural products with their antiviral effects against different viruses. However, adequate research and development are lacking in natural products as anti-CoV agents. Such agents take part and express a crucial role for viral attack prevention which combat CoV.

Herbal Extracts

Several Chinese herbs like *Pyrrosia lingua, Artemisia annua, Lycoris radiata, and Lindera aggregata* extracts showed their anti-SARS-CoV effect with EC_{50} 2.4–88.2 µg/mL (*in-vitro*).[164] Similarly, Toona sinensis aqueous leaf extract is practiced by Chinese healers as a SARS-CoV replication inhibitor, with EC_{50}value within the range of 30-40 µg/mL.[165] Aqueous concentrate of *Houttuynia cordata* act as RdRp and chymotrypsin-like protease (3CLpro) inhibitor of SARS-CoV. It also enhaced cell count (CD4+ and CD8+) in *in-vitro* and *in-vivo*. It produces immune stimulatory effects, which inhibit viral replication.[166] However, significant inhibition produced by methanolic fractions of *Dioscorea batatas* and *Cibotium barometz* with IC_{50} 39 and 44 µg/mL, respectively.[167]

In addition, *Polygonum multiflorum* and *Rheum officinale*, extracts inhibited SARS-CoV spike protein (S) and host protein ACE2 with IC_{50} 1-10 µg/mL (*In-vitro*) and proved entry into inhibitory potential.[168]

Citrus sinensis and *Nigella sativa*, extracts reduced the reproduction of HeLa-CEACAM1a cell (HeLa-epithelial carcino-embryonic antigen-related cell adhesion molecule 1a) and infection was induced with MHV-A59 (mouse hepatitis virus–A59). It also lowered TRP gene expression but enhance intracellular calcium level. However, this effect didnot tally with the viral reproduction lowering effect. However, Anthemis hyalina powerfully inhibit replication of CoV.[169]

Phyto-constituents

Previous reports suggest that a phytagglutinin named concanavalin A (molecular weight 25 kDa) found in jack beans (*Canavalia ensiformis*) actively inhibit CoV. Concanavalin A transiently inhibits, viral envelop glycoprotein hemagglutinin-esterases (HEs) and also inhibits glycosylation of membrane proteins with MIC 10 µg/mL in CoV encephalomyelitis.[170] So it ultimately prevents entry and replication of the virus in the host. It is restricted due to its severe hepatotoxicity in test animals.[171] Further, bromelain a protein-

digesting enzyme from pineapple reduce CoV glycoprotein and its cell viability that isolated from pigs.[168] It can prevent the interaction of SARS-CoV with the host. Lycorine a chemical constituent from *Lycoris radiate* inhibited SARS-CoV with EC_{50} 15.7 nM.[164] Savinin a lignans from *pterocarpus santalinus*,[172] Compound isolated from *Torreya nucifera* compounds such as amentoflavone, apigenin, luteolin, and quercetin are chemically flavones and biflavones that inhibit SARS-CoV 3CLpro with IC_{50} values of 8.3, 280.8, 20.2, and 23.8 μM, respectively.[173] Similarly, black tea phenolic constituents such as 3-isotheaflavin-3-gallate, theaflavin-3, 30-digallate and tannic acid inhibit SARS-CoV 3CLpro with IC_{50}value of 3, 7, and 9.5 μM, respectively.[174]

Omacetaxine mepisuccinate is a alkaloid isolated from *Cephalotaxus fortune* inhibit expression of human corona virus and murine with IC_{50} ~11 nM.[175] From *Tylophora indica* isolated components tylophorine (IC_{50} value of 0.018 μM) and 7-methoxycryptopleurine (IC_{50} 0.005 μM) inhibit S and N protein of CoVs so inhibit their replication and prevent stomach flu associated with them.[176] Cepharanthine an alkaloid isolated from *Stephania cepharantha Hayata* also inhibited protease enzyme of SARS-CoV at 0.5–10 μg/mL concentration.[177,178] Bisbenzylisoquinoline alkaloid component berbamine extracted from the plant *Berbaris amurensis* inhibits HCoV-NL63 with IC_{50} value of 1.48 μM. [179]

A glucoside saikosaponins A, B2, C, and D obtained from *Scrophularia scordonia*, *Bupleurum sp*., and *Heteromorpha sp*. within 5–25 μM/L concentration showed their inhibitory potential in CoV-229E cells with EC_{50} values of 8.6, 1.7, 19.9, and 13.2 μM, respectively.[180] They may prevent penetration and attachment of viruses in humans. Similarly, Isatis indigotica phenolic components such as aloe emodin, sinigrin, hesperetin, β-sitosterol and indigo extracted from *Isatis indigotica* inhibit SARS-CoV 3CLpro with IC_{50} 217, 752, 8.3, 365, and 1,210 μM respectively.[181]

Salvia miltiorrhiza chemical compoundsof tanshinones derived from *Salvia miltiorrhiza* such as rosmariquinone, dihydrotanshinone I and tanshinone I at 1–1000 μM concentration inhibit SARS-CoV PLpro and 3CLpro replication and infection. However, dihydrotanshinone I inhibit with IC_{50} 4.9 and 14.4 μM and tanshinone I inhibit PLpro and 3CLpro with IC50 8.8 and 38.7 μM) respectively.[182] Similarly, scutellarein and myricetin reduce the SARS-CoV 3CL pro effect at 10–0.01μM.[183]

Chemical components extracted from *Broussonetia papyrifera* such as broussochalcone A, broussochalcone B, broussoflavan, kazinol(A-J), 30-(3-methylbut-2-enyl)-30,4,7-trihydroxyflavane, papyriflavonol A, and 4-hydroxyisolonchocarpin, inhibit SARS-CoV PLpro and 3CLpro. Among these components most efficient inhibition displayed by papyriflavonol A against PLpro with IC_{50} 3.7 μM.[184] Similarly, Panax ginseng component gynosaponin C also called ginsenoside Rb1 to inhibit the activity of virus at 100 μM concentration. [185]

The natural isolated compounds from the *Cinnamon cortex* such as cinnamtannin B1, procyanidin A2 and procyanidin B1 inhibit infection of SARS-CoV at 0–500 μM concentration.[186] *Phyllanthus emblica* L. isolated polyphenolic flavonoids or carotenoid compounds such as, tetra-O-galloyl-beta-D-glucose and luteolin within 3-10 mol/L act as S protein inbitor of SARS-Cov-2 and 3CL protease inhibitor SARS-CoV. The major limitation of luteolin is its poor oral absorption show several liposomal formulation of luteolin are developed and mix with olive pomace oil that has additional anti-inflammatory actions of its own. However, a novel luteolin analog, tetramethoxyluteolin, more potently inhibits cytokines (TNF and IL-1β) and chemokines (CCL2 and CCL535) induced mast cells inflammation in human, need its further evaluation. [187]

In another study, isolated compound like psoralidin, corylifol, bavachinin, neobavaisoflavone, isobavachalcone, and 4'-O-methylbavachalcone isolated from *Psoralea corylifolia* Psoralea corylifolia isolated compound like psoralidin, corylifol, bavachinin, neobavaisoflavone, isobavachalcone and 4'-O-methylbavachalcone inhibit papain-like protease of SARSCoV. Among them psoralidin showed powerful inhibition of SARS-CoV protease with IC_{50} 4.2 μM.[188] *Cassia fistula* components emodin, chrysin and rhein inhibit S protein and ACE2 of SARS-CoV in between 0–400 μM concentration.[189] Although, isolated products from *Ecklonia cava*such as phlorofucofuroeckoln, eckol, dieckol, and 7-phloroeckol inhibited to porcine epidemic diarrhea virus cells with IC_{50} values of 12.2, 22.5, 14.6 and 18.6μM, respectively.[190]

Juglanin a cyclic ketone from seed husks of walnuts of *Juglans regia* blocks SARS-CoV 3a channel with IC_{50} value of 2.3 μM.[191] Isolated compounds from *Paulownia mentosa* such as 30-O-methyldiplacol, 40-O-methyldiplacol, tomentin (A-E), 30-O-methyldiplacone, 40-Omethyldiplacone, 6-geranyl-40,-5,7-trihydroxy-30,50-dimethoxyflavanone, diplacone, and mimulone inhibit papain like protease (PLpro) of SARS-CoV within 0–100 μM concentration.[192] Similarly, RNA oligonucleotide nanoparticle obtained from teas components (−) gallocatechin gallateand (−) catechin gallate inhibited N protein of SARS-CoV at 0.001–1 μg/mL concentration.[193] On the other hand, isolated compounds like quercetrin, quercetin, cinanserin and rutin, from *Houttuynia cordata* at 15.63–500 μg/mL act against murine CoV.[194]

Fruits and twigs of *Aglaia foveolata* isolated compound sivestrol showed potent cytotoxicity against various cancer cell lines of human. This compound inhibited translation of viral mRNA of HCoV-229E at 0.6–2 μM range with IC_{50} of 40 nM.[195] Similarly, a natural phenol ferruginol having a substructure of terpenoid obtained from redwood *Sequoia sempervirens* needles showed its antitumor potential in breast, colon, and lung cancers of human and also act as significant replication inhibitor of SARS-CoV.[196]

Isolated compounds of *Tylophora indica* (Tylophorine and 7-methoxycryptopleurine) act as CoV replication inhibitor in swine testicular cells infect with IC_{50} 58 nM and 20 nM, respectively. Tylophorine inhibits replication of RNA and NF-κB (JAK2-mediated) in CoV cell at 0–1000 nM concentration.[197]

Many compounds from several species of plant like betulonic, betulinic acid, hinokinin, 8β-hydroxyabieta-9(11),-13-dien-12-one, savinin 3β, 12-diacetoxyabieta-6, 8, 11, 13-tetraene and curcumin act as replication inhibitors of SARS-CoV within 0–80 μM range.[198] Ouabain from bovine hypothalamus acts as a viral RNA replication inhibitor (Inhibit viral clone number) within 0–3000 nM range.[199] Recent findings showed that lycorine (different species of Amaryllidaceae), emetine from *Cephaelis ipecacuanha* inhibit the division process of cells and also inhibit the synthesis of DNA, RNA of MERSCoV, MHV-A59HCoV-NL63 and HCoV-OC43 within 0–5 μM concentration.[179]

Marine alga *Halimeda tuna* produce a diterpene aldehyde component halituna, inhibit murine coronavirus.[200] Another marine alga *Streptomyces hygroscopicus* component hygromycin B dose-dependently inhibits replication of MHV-A59 cell (mouse hepatitis virus-A59) and also inhibit necrosis based foci of the liver.[201]

Bacterium *Streptomyces parvulus*, antibiotic compound actinomycin D inhibits penetration and attachment of CoV at 5–25 μM concentration with EC50 0.02 μM.[202] Mycophenolate mofetil obtained from the fungi *Penicillium brevicompactum, Penicillium stoloniferum*, and *Penicillium echinulatum* inhibit the division of cell and also inhibit synthesis of DNA, RNA in MERSCoV, MHV-A59, HCoV-NL63 and HCoV-OC43 in between 0–5 μM concentration, produce immune-suppressant effect on the CoV species.[179]

Current Treatment Procedure in COVID-19

At present specific therapy not available against COVID-19 pneumonia. Management includes transmission prevention, complications prevention, and provides supportive care. Oxygen is immediately given to patients who undergo the problem of respiratory distress (ARDS). Fluid resuscitation not required if there is no sign of hypoperfusion of tissue, as it may worsen the status of oxygen or shorten the duration of ventilation and produce lungs edema. Systemic corticosteroids are not suggested because they delay viral clearance.[203]

Precautionary measure taken in COVID-19

It takes several precautionary measures for patients in suspected or known COVID-19 pneumonia. All professionals of the healthcare system caring for the patient of COVID-19. It suggests respiratory and eye protection. We consider droplet precautions withdrawal. if chest radiography and successive two RT-PCR test results, from a clinically recovered patient, show negative in at least 24 h interval. However, some patient test results show negative but a few days later, test results show positive consideration as viral carriers.[204] Thus the decision for droplet precautions against withdrawal depends on judgments and evaluation of clinicians, but not dependent on clinical, laboratory and radiological confirmation. Although asymptomatic patients close contact were not infected but quite regarded as viral carriers. The COVID-19 pneumonia infected cases are infectious before the disease onset and after treatment. Thus, there is a need to re-evaluate the hospital discharge norms and quarantine norms to achieve adequate disease control.

Recommendations in COVID-19

Recently, March 13, 2020 WHO clinical management guidance document or Centers for Disease Control and Prevention highlight the importance of supportive therapy/care based on intensity of illness, ranging from symptomatic treatment for mild disease cases to ventilatory management for ARDS and early identification and treatment of viral infections and sepsis in critically ill patients. Further, it also states that still now available COVID-19 treatment has no specificity. Corticosteroids are avoided or not routinely given. Investigational therapeutics, specifically remdesivir, is mentioned as options through either ongoing clinical trials or compassionate use. Based upon this, the WHO recently declare to launch a worldwide "mega trial" called SOLIDARITY.[205] It is a realistic trial design that will randomly use in confirmed cases with standard care of lopinavir and ritonavir combination alone or lopinavir and ritonavir combination with remdesivir or lopinavir and ritonavir combination with interferon-β and use of chloroquine or hydroxychloroquine. In this trail, drug application mainly based on locally available drugs.

Although, pharmacological or clinical management is important in COVID-19 but now self-isolation, social distancing, wearing of mask and development of self-immunity by nutraceuticals with yoga and pranayam are other parameter to prevent COVID19. We conclude it that quick epidemiologic tracking, diagnostic testing and preventive development and appropriate therapeutic strategies are required for SARS-CoV-2 viral genome.

Limitation and Conclusion

This review has several limitations, like Few clinical trials mentioned, mostly comprises descriptive reports and case series from China and other countries affected early in this pandemic recommendations thus relevant international data could lack and research findings are constantly developing as fresh evidence arises. Further, the treatment data to date derive from small clinical trials (not over 250 patients). There is bias of treatment effect. It mainly focused only on adult patients but may not apply for a pediatric patient. Outcomes including fatality case-rates must be clarified. This paper addressed numerous aspects concerning nCOVID-19 and its interaction with other coronavirus diseases, and the function of various approaches in the control and prevention of nCOVID-19. In particular, there are actually no COVID-19 vaccines or unique antiviral medicines. All the medications prescribed come from information gained during the diagnosis of MERS, SARS or other coronavirus families. More analysis is required to show the efficacy of such medicines.

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