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A COMPREHENSIVE REVIEW ON CURRENT ASPECTS OF COVID-19

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ABSTRACT

COVID-19 (coronavirus disease 19) is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China and spread around the world. There were continuous rise in number of COVID-19 cases worldwide which further declared as pandemic situation by WHO to the world. On 16 may 2021 more than 17,175,658 active cases were present in world. In this review we discussed about epidemiological characteristics, pathophysiology, diagnostics method, available treatment measures, still there is no specific treatment available for COVID-19. Also we discussed preventive measures including various Vaccine development strategies which are been used in the development of COVID-19 vaccine along with vaccine candidates.

KEYWORDS: COVID, EPIDEMOLOGY, Pathophysiology & TREATMENT.

INTRODUCTION

COVID-19 pandemic outbreak was initiated from the Wuhan, Hubei province, China and rapidly infected many peoples in December 2019.[1] On December 2019 first patient was hospitalized .Patient with cases of pneumonia with unknown etiology were identified in Wuhan on December 30. A global health emergency declared based on growing cases rates at Chinese and international locations by WHO Emergency Committee on January 30, 2020.[2] On March 11, the World Health Organization declared COVID-19 as a pandemic state to the whole world.[3] The World Health Organization (WHO) officially named the disease 'COVID-19'. The International Committee on Taxonomy of Viruses named the virus 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2).[4] Coronaviruses belong to the Coronaviridae family in the Nidovirales order. Because of crown like spike's protein on outer surface it was named as coronavirus. Coronaviruses size ranging from 65-125 nm in diameter and 26-33kbs in length, contain a ssRNA as a nucleic material. The subgroups of coronaviruses family are alpha, beta, gamma and delta coronavirus.[5,6] Various human coronaviruses till known are classified in (Fig.2). Several members of the family Coronaviridae constantly circulate in the human population and usually cause mild respiratory disease.[7] Until SARS-CoV emergence in 2002 in Guangdong, China these viruses were thought to infect only animals until the world witnessed a severe acute respiratory syndrome (SARS-CoV). In 2012 another pathogenic coronavirus, named as Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak caused an endemic in Middle Eastern Countries.[6] Recently emerged novel SARS-CoV-2 virus (Fig.1) belonging to the genus beta coronavirus, it is a positive sense ssRNA virus and this virus is enveloped.

SARS-CoV and SARS-CoV-2 both viruses uses host cells angiotensin converting enzyme 2 (ACE2) receptor of for entry into cells of host and both are homologous to each other.[8] SARS COV-2 consist two large and several other ORF (open reading frames)which are code for several structural and non-structural proteins. 16 non-structural proteins are coded by two large ORF. Four structural proteins (S) spike, (N) nucleocapsid, (M) membrane, (E) envelope and nine accessory proteins expression by other ORF.[9]

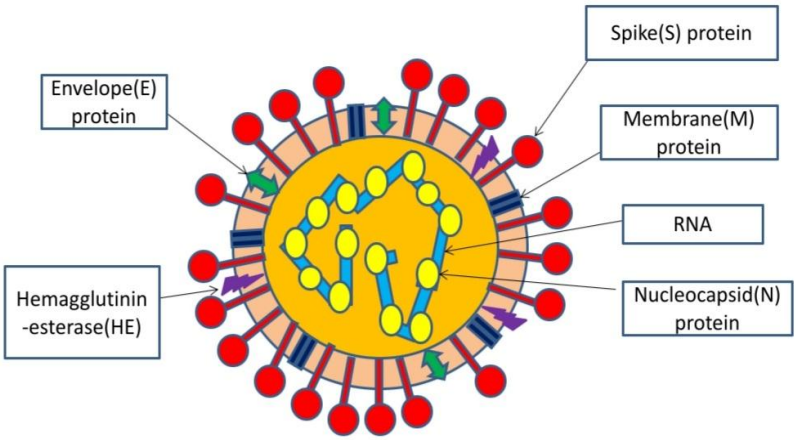

Fig. 1: Schematic representation of SARS-COV-2 with structural proteins.

EPIDEMOLOGY OF COVID-19

In Hubei Province, Mainland China during December 2019 cluster of cases with pneumonia of unknown etiology was found which are epidemiology connected with Wuhan seafood market.[10] Initially it was supposed that SARS-COV-2 is spread to the peoples who had visited the seafood market or consumed the food prepared from infected animals of seafood market. But some patient of COVID-19 with no history of travelling to seafood market of Wuhan was detected. Then contact tracing and analysis of that COVID-19 patients shows the possibility of human to human transmission of COVID-19. Later epidemiological studies confirmed that COVID-19 spread from patients to their family member or person with close proximity and they also got infected with COVID-19 even though they were not visited the seafood market.[11]

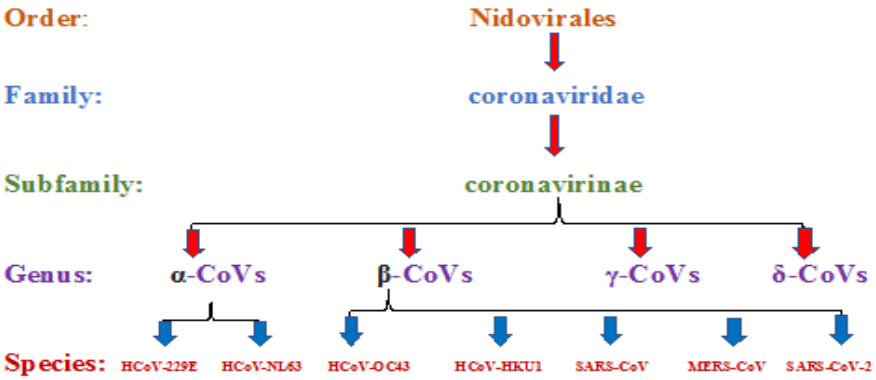

Fig. 2: Classification of coronaviruses.

Until December 5, 2020, more than 66 million cases and more than 1.5 million death due to COVID-19 infection has been reported globally.[12] As of March 22, 2021, COVID-19 highly infectious disease has spread to 223 countries and territories, with 122 822 505 confirmed cases with 2 709 041 deaths worldwide.[13] Statistics of cases and death due to Covid-19 till 15 may 2021 were summarized in Table.1.

Table 1: Statistics of cases and death due to COVID-19 till 15 May 2021 as per WHO.

Sr.no	Name of country	Total cases	Total death
1	USA	32534073	578984
2	India	24372907	266207
3	Brazil	15433989	430417
4	France	5754154	106666
5	Turkey	5095390	44301
6	Russia	4931691	115480
7	United kingdom	4446828	127668
8	Italy	4146722	123927
9	Spain	3598452	79281
10	Germany	3242103	86025

Infection Source
SARS-COV, MERS-COV, SARS-COV-2 are the coronavirus that Spread from zoonotic source to humans through intermediate host species.[11] But currently, potential source of infection are COVID-19 patients. Asymptomatic patients are one of the potential source of infection also sever patients are more likely responsible for spread of SARS-COV-2 in human population.[14]

Incubation Period
The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days.[12]

Mortality Rate
Combined case mortality rate for SARS-CoV-2 was 2.3% which is less compared to SARS-COV and MERS-COV 9.6% and 34% respectively. Rate and cases of mortality is vary based on age group, any medical comorbidities etc. Mortality of patients with age group more than 65 was higher as per case report of Italy and it was 7.2%.[15,16]

Transmission
Transmission among humans: SARS-COV-2 transmission is by direct or indirect contact of normal people with infected patients. The most common mode of SARS-COV-2 transmission is through droplet. Infected patients during taking, coughing, sneezing expels droplet in form of aerosols in surrounding and on the healthy people, it is one of the mode via healthy people get infected and virus get transmitted from person to person. Also long term exposure with symptomtomatic people, or with COVID-19 patients. Another possible mode of transmission is through surface contact, these are the surfaces (e.g. any metal /rubber/plastic, soil, water etc.) which are previously touched or exposed by COVID-19 affected patients.[17,18]

Clinical Manifestation
Sign and Symptoms: Most common and specific signs and symptoms includes cough, shortness of breath, fever, fatigue, anorexia, tachycardia, change in oxygen level. Some non-specific signs and symptoms are as follows-nasal congestion, anosmia, ageusia, sore throat, headache, nausea, vomiting, diarrhoea.[19,20]

High risk group of people: Older age patients (age more than 60 years) and patients with underlying medical co-morbidity like diabetes, hypertension, cardiovascular disease, chronic lung and respiratory disease, cancer, cerebrovascular disease, dementia, mental disorders, chronic kidney disease, immunosuppression, obesity etc. As well as pregnancy and related conditioned people are part of high risk group.[19,21]

Severity of Infection
Clinical manifestation of SARS-COV-2 infected patients is vary for patient to patient from no symptoms to critical illness. Also patients may shows changes in their clinical manifestation over time, so severity of COVID-19 disease is categorised as:

Asymptomatic /Presymptomatic COVID-19 illness: Patient does not have an symptoms associated with of SARS-COV-2 infection but have positive diagnostic test for COVID-19.[20]

Mild COVID-19 illness: COVID-19 patient showing signs and symptoms like cough, fever, sore throat, headache, nausea, vomiting, diarrhoea, anosmia and ageusia etc. But not showing signs and symptoms like dyspnea, shortness of breath. Upper respiratory tract infection without pneumonia. Also no abnormalities in chest X-ray, chest CT.[22]

Moderate COVID-19 illness
Patients with on room air oxygen saturation ($SpO2 \geq 94\%$ at moderate covid-19 illness. Radiographic imagining indicate evidence for lower respiratory disease.[12]

Sever COVID-19 illness
Patients of this category need oxygen therapy because their on room air level of $SpO2 < 94\%$. Also they show higher breathing rate >30breaths/min, ratio of $PaO2/FiO2 < 300$ mm Hg (arterial partial pressure of oxygen to fraction of inspired oxygen), lung infiltrates >50%.[12]

Critical COVID-19 illness
Patients who shows acute respiratory distress syndrome may lead to respiratory failure, septic shock, disfunctioning of cardiac, hepatic, renal etc. systems i.e. multiple organ dysfunction, cytokine storm and these cases require life saving therapies like mechanical ventilation.[23]

SARS COV-2 Variants
SARS-CoV-2 with one or more new mutations is referred to as a "variant" of the original virus.[24] An unexpected rise in reported of COVID-19 cases in December, 2020, it was due to the emergence of the new SARS-CoV-2 variants. Original strains have evolved to new strain, and new variants with increased transmission rate compared to the original strains, which makes COVID-19 even more challenging. Different variant were found are 501Y.V1 (B.1.1.7) in the UK, 501Y.V2 (B.1.351) in South Africa and 501Y.V3 (B 1.1.28) Brazil.[25-27] Both variants 501Y.V1 and 501Y.V2 show N501Y mutation in spike proteins receptor binding domain, also 501Y.V2 variant shows E484K and K417N mutations too. 501Y.V3 (P.1) shows N501Y, E484K, and K417T mutation. Because of this mutation these all variants are more virulent and shows high transmission rate.[25]

SARS-COV-2 Variants of Interest
SARS-COV-2 with mutation in genome causing changes in phenotype compared to a reference isolate and shows

community transmission, multiple COVID-19 cases in multiple countries.[28] Variants of interest are B.1.526, B.1.526.1, B.1.525, P.2, B.1.617, B.1.617.1, B.1.617.2, B.1.617.3.[29]

SARS-COV-2 Variants of Concern

SARS-COV-2 with harmful changes in epidemiological characteristics, increase in transmission ability, with high virulent character changes in clinical disease characteristics, also shows decrease in effectiveness towards diagnosis, therapy, vaccines and other public health and social measure.[28] Variants of concern are B.1.1.7, P.1, B.1.351, B.1.427, B.1.429.[29]

Pathophysiology of Covid-19

During the early course of infection, cells of nasal and bronchial epithelium and pneumocytes of host are target of SARS-CoV-2. SARS-COV-2 consists trimeric spike protein(S) with two subunits: S1 receptor binding subunit and S2 fusion subunit. Virus attach to the host cells through its spike proteins S1 subunits receptor-binding domain (RBD) which binds to angiotensin-converting enzyme 2(ACE2) receptor of host cell. Host cells serine proteases TMPRSS2 (transmembrane protease serine 2) is used by SARS-COV-2 for priming of spike protein(S) and infecting target cell which promote uptake of virus by fusion and uncoating by cleaving ACE2,[18,30,32] Along with TMPRSS2, the endosomal/lysosomal cysteine proteases cathepsin B and L responsible for virus entry in the cell. Another protease furin protease is also involved in the infection process of SARS-CoV-2 and potentiates SARS-CoV-2 infectivity, providing a pathway to enter into the central nervous system.[33] After entering of into host cells SARS-COV-2 RNA uses host cells machineries to produce viral genome and polypeptide chain and form replication-transcription complex which is required for formation of sub-genomic RNA and structural proteins(S,M,E,N).[34] Assembly of genome RNA and viral proteins into mature virions in the endoplasmic reticulum(ER) and Golgi apparatus followed by transportation via vesicles and mature viral progeny is released out of the cell by exocytosis.[6,35] After exocytic release of viral progeny some virus may enter in blood stream, causing viremia. Now virus spread and affecting different body organs which consists ACE2 receptor.[35] The alveolar cells, ciliated and goblet cells in the airway tract are highly expressed with ACE2 receptor, so virus easily get entry into the cells of respiratory system of host, hence pneumonia is a one of prominent clinical manifestation of COVID-19. Also ACE2 receptor is present on vascular endothelium, cardiac sells and intestinal epithelium hence COVID-19 patients shows cardiovascular complications, gastrointestinal complications. Even monocytes and macrophages are expressed with ACE2 receptor.[32] Lungs shows microscopic bilateral diffuse alveolar damages, cellular fibromyxoid infiltrates and interstitial mononuclear inflammatory infiltrates.[36] As per hospitalized patient data, about 80% COVID-19 cases presented with asymptomatic or with mild symptoms while the remainder are severe or critical.[37] For such sever and critical patients normal immune responses is disrupts due to COVID-19. Which leads to impaired immune system and uncontrolled inflammatory responses. In such patients high cytokine levels, and an increase in immunoglobulin (IgG) and total antibodies, lymphopenia, lymphocyte activation and dysfunction, granulocyte and monocyte abnormalities are observed.[38]

Escape of SARS-COV-2 from immune system

SARS-COV-2 inhibits tumor necrosis factor (TNF) receptor associated factors (TRAF) 3and 6, which are center for induction interferon regulatory factor 3/7 (IRF 3/7)which cause release of type 1 interferon (T1 IFN)in response by Toll-like receptors (TLR 3 and 7) and or cytoplasmic RNA sensors namely retinoic acid inducible gene I (RIG-I) and melanoma differentiation associated proteins 5 (MDA-5) which are pattern recognition receptors (PRRs) for detection of RNA virus on our immune cells, but because of SARS CoV-2 inhibits mitochondrial antiviral signalling protein leading to escape of virus from immune system recognition. By phosphorylation of STAT family transcription factor by SARS-COV-2 inhibit T1IFN signalling so it escapes from immune system recognition.[32]

Cell mediated adaptive immune response

Infected host cells get died by exocytic release of new viruses together with intracellular components of infected cells that trigger innate inflammatory mechanism. Now virus get detected by immune system because of T1 IFN and as a result of it, hosts defence against virus get activated by adaptive immune response. CD4+ and CD8+ T cells efficiently promote specific adaptive immune response, CD4+ T cell promote cytokines, CD8+ T cells and natural killer(NK) cells mediate cytotoxicity.[39,40]

Antibody mediated response

After viral infection within 7-14 days IgM antibodies starts to appear and shows gradual decrease with disease progression and IgG appear after 14 days and remain for long time. As per one study antiviral antibodies IgG, IgM takes about an average 13 days from start of symptoms.[35,41] Even neutralizing antibodies have important role as host defence mechanism against SARS-CoV-2, they plays a protective role by limiting infection at later phase and prevents reinfection in the future, though there is risk of exaggerated inflammatory response with release of large quantities of IL-6, IL-8, and recruitment of inflammatory cells to the lung due to activation of FcϒR in M2 macrophages by neutralizing antibody binding to S protein of SARS-CoV-2 in the lung. This trigger of exaggerated inflammatory response by antibodies through a process called as antibody dependent enhancement (ADE).[37,42,43]

Cytokine storm

Upon infection with SARS-CoV-2, CD4+ T cells can be rapidly activated into pathogenic T helper (Th) 1 cells

that secret granulocyte-macrophage colony-stimulating factor (GM-CSF), which further induces CD14+, CD16+ monocytes, virions inhibit type 1 IFN signalling in infected macrophages while allow proinflammatory IL-1, IL-6, IL-12, IL-18and TNF α expression, which may contribute to hyper inflammation and cytokine storm syndrome.[44,45]

Further recruitment of monocytes/macrophages and neutrophils due to inflammatory cytokine IL-17 produced by Th17 to the site of infection and stimulate cascade of other cytokine.[47] Resulting in hyper inflammation and cytokine release syndrome (CRS). The transition from milder symptoms to acute respiratory distress syndrome (ARDS) is likely due to an unrestrained cytokine release by the hyperactive immune response.[46]

Diagnostic Methods

1. Molecular method

WHO recommend the NAAT (Nucleic Acid Amplification Technique) for detection of SARS-COV-2 in suspected individuals. Example RT-PCR, this technique detect viral RNA from samples obtained from upper or lower respiratory tract (nasal, pharyngeal swab, brochoalveolar lavage), saliva of COVID-19 suspect. Result-Positive RT-PCR test indicate, presence of SARS-COV-2 in suspected individual. Disadvantages are expensive, time consuming, require skilled professional technician etc. Also having advantages like high sensitivity and specificity.[48,51]

2. Antigen Detection Test

This technique detect the presence of antigen most often (N) Nucleiocapsid protein of SARS-COV-2 from the nasopharyngeal swab. Advantages are easy, fast result, low cost. Disadvantages are lesser sensitivity and specificity lower than NAAT.[48,52,53]

3. Chest Computed Tomographic Findings

Chest CT examination is important tool in diagnosing COVID-19 and also used for monitoring and evaluation of disease progression and therapeutic efficacy. Chest CT finding for covid-19 affected patient-Ground glass opacity (GGO), Consolidation, Reticular pattern, Crazy paving pattern, Air bronchogram, Airway changes, Pleural changes, curvilinear line, Fibrosis, Vascular enlargement, Air bubble sign, Nodules, Halo sign, Reversed halo sign or atoll sign, Lymphadenopathy, Pericardial effusion. These chest manifestation can shows variation in different individual and as per stage of disease. Most commonly Bilateral GGO and Consolidation were taken as predominant radiological findings for Covid-19 patients.[54]

4. Chest X-ray (CXR)

CXR FINDINGS: GGO, Pulmonary nodules, Interstitial changes, Bilateral pneumonia, Post inflammatory focal atelectasis are radiologic diagnostic findings through CXR for covid-19 suspect. Advantage are easy availability compared to CT. Disadvantages are lesser specificity compared to Chest CT.[55]

Treatment

In Current situation, there are no specific antiviral drugs for the control of SARS-CoV-2 induced COVID-19 disease. Symptomatic treatment strategies are recommended for clinical practice to alleviating clinical symptoms by general and symptom-specific supportive care.[16,56] Drug molecules binding to the virus, inhibitors that can target specific enzymes involved in viral replication or viral transcription are potential therapeutic options against COVID-19.[56] Here, we summarize potential therapeutics currently available for the treatment of SARS-CoV-2.

Antiviral agent

Remdesivir

Currently, Remdesivir is FDA approved drug for the treatment of COVID-19 in hospitalized adult and paediatric patients (aged ≥12 years and weighing ≥40 kg). Also for paediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg for emergency use through an FDA Emergency Use Authorization (EUA).[12] Remdesivir is a prodrug. IT is an intravenous nucleotide prodrug of an adenosine analog.[59] Upon metabolism of monophosphoramidate adenosine analogue prodrug(Remdesivir) it convert to an active tri-phosphate form that inhibits viral RNA synthesis.[58] By binding to viral RNA-dependent RNA polymerase(RdRp), it inhibiting viral replication through premature termination of RNA transcription.[57] In a randomized controlled clinical trial (NCT04280705) by Allergy and Infectious Disease (NIAID) on 1063 patients, in primary results remdesivir treated group shows the median time to recovery was 11 days and 15 days for placebo treated group, with 8% mortality in remdesivir group as compared to 11.6% in placebo group ($p = 0.059$). Results of this trial support the use of remdesivir in hospitalized COVID-19 patients, and those require supplemental oxygen therapy.[59]

Adverse effects are widely ranged from rash, diarrhea, increased liver enzymes to sever condition like multiple organ failure, hypotension septic shock, and acute kidney injury.[60]

Favipiravir

Favipiravir is a pyrazine-derived nucleoside analog which is a broad-spectrum antiviral. It is a prodrug which upon converts into active form Favipiravir ribofuranosyl-50-triphosphate that selectively inhibits the RdRp.[61,62] In vitro studies on Favipiravir shows that it is a potent against SARS-CoV-2 with EC50=61.88μM. A clinical trial on 80 patients was conducted in Shenzhen hospital was show that Favipiravir has stronger antiviral effect than lopinavir and ritonavir.[57,63]

Adverse effects are diarrhea, chest pain, nausea, increased hepatic enzymes, and changes in uric acid in

the blood. In pregnancy may cause teratogenicity and embryo toxicity in animal studies, hence contraindicated in pregnancy.[61,62,64]

Chloroquine (CQ) and Hydroxychloroquine (HCQ)

Chloroquine and hydroxychloroquine is used in treatment and prevention of malaria from a long time, also as anti-inflammatory for systemic lupus erythematosus and rheumatoid arthritis.[63,65] Hydroxychloroquine is an analogue of chloroquine with less severe side effects. Along with this activity both drug have potential broad-spectrum antiviral activities. CQ and HCQ both has activity against SARS-COVs as per in vitro studies.[63,66] They block viral entry into host cells by inhibiting glycosylation of host receptors, cause rise in endosomal pH and inhibiting endosomal acidification, which is required for virus-host cell fusion, and inhibit proteolytic processing which leads to inhibition of viral replication. Along with this both agents have immunomodulatory effects like decrease in cytokine production and inhibition of autophagy and lysosomal activity in host cells.[63,66,68]

CQ phosphate was used in 100 patients of COVID-19 in China, results shows that it could effectively control and inhibit pneumonia. A study of an open-label non-randomized clinical trial of HCQ on 36 COVID-19 patients showed that the addition of azithromycin to HCQ provides better viral clearance compared to HCQ.[63,69] However, in a recent study, hydroxychloroquine was not effective against COIVD-19 patients and has been revoked from the emergency use against COVID-19 patients due to safety concerns. Both agents can cause rare and serious adverse effects (<10%), including QTc prolongation, hypoglycaemia, neuropsychiatric effects, and retinopathy.[70,71]

Lopinavir and Ritonavir

Lopinavir and ritonavir are protease inhibitors and are approved drugs for HIV. Also lopinavir and ritonavir reported with antiviral activities against SARS and MERS.[72,74]These protease inhibitors binds to M^{pro}, a key enzyme that are responsible for proteolytic cleavage and prevent viral gene replication.[51,75] In the United Kingdom a large randomized clinical trial on Lopinavir/ritonavir in hospitalized patients with COVID-19 was done but not demonstrate clinical benefit. Also in another large international randomized trial, mortality rate of hospitalized patients with COVID-19 was not reduce with lopinavir and ritonavir.[76,77] Because of unfavourable effects and negative clinical trial data, recommendation against the use of lopinavir; ritonavir or other HIV protease inhibitors was given by the NIH COVID-19 treatment guidelines.[12] Adverse effects are vomiting, diarrhea, hepatotoxicity, Bradycardia, Risk of cardiac arrhythmias (e.g., QT prolongation).[60,64]

Adjective Therapy

Corticosteroids

WHO strongly recommends use of systemic corticosteroids (for 7 to 10 days) to treat patients with severe or critical COVID-19; but suggests against use of-corticosteroids in patients with non-severe COVID19.[78] Those hospitalized patients who require supplemental oxygen but not on high-flow oxygen and also patients who require oxygen through a high-flow device, non-invasive ventilation, mechanical ventilation, or ECMO (Extracorporeal Membrane Oxygenation). For such patients dexamethasone in combination with remdesivir is recommended. If remdesivir cannot be used, dexamethasone may be given as monotherapy.[64] Results of a meta-analysis of clinical trial on dexamethasone demonstrated that, compared with placebo, corticosteroid therapy reduced the risk of mortality and duration of mechanical ventilation.[79,80] Adverse effect are sepsis, acute respiratory distress syndrome (ARDS) and community-acquired pneumonia (CAP), increasing the incidence of hyperglycaemia and hypernatremia are some of the potential harmful effects of corticosteroids.[58]

Convalescent Plasma Therapy

In a retrospective analysis, convalescent plasma therapy shows reduction in mortality and shortening hospital stays with SARS infected patients.[81] Apheresis technique is used to isolated plasma containing antibodies against SARS-CoV-2 then by checking and matching the ABO compatibility plasma transfusion in COVID-19 patients is done. Plasma obtained by apheresis contain neutralizing antibodies along with clotting factors, anti-inflammatory cytokines, and other natural antibodies which provide supportive role to immunomodulatory benefits of convalescent plasma therapy.[82] Plasma from donors who have recovered from COVID-19 may contain antibodies against the SARS-CoV-2 in their plasma and administration of this plasma containing anti SARS-COV-2 antibodies to another patient limit viral reproduction in the acute phase of infection and help to clear the virus. That may help suppress the virus and modify the inflammatory response. Potential benefits include improvement in symptoms, reduced need for supplemental oxygen or mechanical ventilation, and reduced mortality.[83,85] Side effects are risk of allergic or anaphylactic reaction, febrile non-haemolytic reactions, haemolytic reactions, transmitting infections, transfusion-associated circulatory overload, transfusion-related acute lung injury, post transfusion purpura, hypothermia, and metabolic complications.[85]

Anticoagulant

The incidence of pulmonary thrombosis in Critically ill COVID-19 patients was reported as high as 30% and 1.3% in non- COVID-19 patients.[86] During COVID-19 pathogenesis coagulative and fibrinolytic abnormalities were observed which affect medical condition of patients Therefore, an interim guidance is issued by the

International Society on Thrombosis and Haemostasis (ISTH) which recommends the measurement of platelet count, D-dimer, fibrinogen and prothrombin time in all COVID-19 patients.[87] Occurrence of venous thromboembolism in hospitalized patients with COVID-19 was found to be 14.1% as per a meta-analysis of studies.[88] Anticoagulant recommended for prophylaxis of venous thromboembolism, pulmonary thrombosis in hospitalized COVID-19 patients are LMWH (Low molecular weight heparin) or fondaparinux than unfractionated heparin.

For critically ill COVID-19 patients LMWH is recommended over unfractionated heparin.[89] Hospital mortality rate was 29.1% for anticoagulant treated patients and 62.7% for those who did not among the 395 critically ill patients which are on mechanical ventilation.[86]

Janus kinase inhibitor

Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins. They inhibit immune activations and inflammation (pro-inflammatory cytokines like IL-6) hence they are anti-inflammatory to control cytokine storm.[90,92] Along with anti-inflammatory effect JAK inhibitors, particularly baricitinib, prevent virus entry and infection into host cell hence have direct antiviral activity through interference with viral endocytosis.[93]

Interleukin-1 (IL-1) Antagonists

In COVID-19 patients level of endogenous IL-1 is elevated and lead to cytokine storm and macrophage activation syndrome. IL-1 antagonists e.g. anakinra inhibit the binding of IL-1 (mediator for inflammatory and immunological response) to its IL receptor, decrease the inflammatory response.[94,96]

Interleukin-6(IL-6) Receptor Antagonists

IL-6 level is elevated in COVID-19 patients, which is a pro-inflammatory cytokine.[97] Clinical trial on human IgG1 monoclonal antibody sarilumab shows that sarilumab binds specifically to IL-6 receptor and inhibit IL-6-mediated inflammatory response.[98]

Prevention

Till the date there is no specific treatment for COVID-19, so that safety measures are the one that could possibly reduce the infection spread and mortality due to SARS-COV-2 .Hence preventive and precautions related measure have a lot of importance to fight against COVID-19.

Various preventive measures are

- Wash hands regularly with soap and water for at least 20 seconds or alcohol based hand sanitizer.
- Avoid close contact by staying 6 feet apart and don't gather in large group.
- Cover your mouth, nose with tissue while coughing and sneezing.
- Wear a face mask if you are going outside of home, also if you feel sick.
- Clean and disinfectant frequently touched objects and surfaces.
- Stay home and stay isolated if you are sick.
- Vaccination is also a one preventive measures against COVID-19. As there is large numbers of increase in COVID-19 cases worldwide, so efforts are been taken to develop vaccine against COVID-19.

As per WHO on 16 May 2021, 99 vaccine candidates are in clinical trials and 184 in preclinical trials.[99] Now we will take a look on various strategies to develop vaccines against COVID-19 and those candidate vaccine who got approval for emergency use.

1. Attenuated vaccines

For development of such vaccine exhaustively long cell or animal cultures of SARS-COV-2 are required. The SARS-CoV-2 virus need to undergo mutations so that it helps virus to adapt for the new host that is culture cell and potentially impair its virulence in the human host, now we get genetically weakened version of the virus, and this process can take years. If SARS-CoV-2 has been weakened by attenuation so it can not cause COVID-19 disease. Still this attenuated virus still having ability to replicate in vivo but with limited disease. Attenuated vaccine effectively stimulates immune system and inducing a strong and persistent immune response to virus. Still attenuated vaccine have disadvantage like Safety issue regarding immunosuppressed peoples and chances of side effects due disease due to attenuated virus but are minor one.[100,101]

2. Inactivated vaccine

The SARS-CoV-2 is inactivated by exploiting different chemical techniques. Vaccines based on killed microorganisms (inactivated vaccines).[101] Physical or chemical approaches are done to make inactivated viruses non-infectious. Chemicals like formaldehyde and beta-propiolactone are used to inactivate the virus. Efficacy of inactivated vaccines is also depends on multiple doses or adjuvants.[102,103] Factors like stabilization of live virus structure in the dry form, separate supply of the solvent, and cold-chain transportation affects it cost and production. Though this type of vaccine are less effective but having higher stability as an advantage.[104]

- COVAXIN (BBV152) developed by Bharat Biotech/ Indian Council of Medical Research/ National Institute of Virology/ Ocugen/ Precisa Medicamentos, current stage of development- Phase III (NCT04641481, NCT04918797).
- KoviVac, an inactivated whole-virion coronavirus developed by Chumakov Federal Scientific Center for Research and Development of Immune and

Biological Products of the Russian Academy of Sciences, current stage of development- Phase III.

- QazCovid-in developed by Research Institute for Biological Safety Problems, Republic of Kazakhstan, current stage of development- Phase III (NCT04691908).
- BBIBP-CorV developed by Beijing Institute of Biological Products/ Sinopharm, current stage of development- Phase III (NCT04510207, ChiCTR2000034780, NCT04612972, NCT049 17523, NCT04560881).
- Inactivated vaccine developed by Wuhan Institute of Biological Products/ Sinopharm, current stage of development- Phase III (NCT04885764, NCT04510207, ChiCTR2000034780, NCT046129 72, ChiCTR2000039000).
- CoronaVac developed by Sinovac/ Instituto Butantan/ Bio Farma, current stage of development- Phase III (NCT04800133, PHRR210210-003308, NCT04942405, NCT04651790, NCT04456595, NCT04508075, NCT04582344, NCT04617483).
- Inactivated SARS-CoV-2 vaccine, vero cell developed by Shenzhen Kangtai Biological Products Co., Ltd. Current stage of development- phase III (NCT04852705).

3. Subunit Vaccines

3.1 Protein subunit vaccine

Instead of using whole microorganisms, purified surface antigens of microorganisms is used to develop subunit vaccines with use of different carriers which serve as a transporter for those antigens. In the anti-SARS-CoV-2 subunit vaccines, the antigens are represented by viral proteins, peptides, or nanoparticles.[102] Conventional cultivation processes, recombinant DNA technology are method to obtaining surface antigens.[105] Because of relatively low immunogenicity of the subunit vaccines, adjuvants are required to generate a vaccine induced stronger immune response. Biological half-life may enhanced by adjuvants.[106,107] Anti-SARS-CoV-2 subunit vaccine uses S protein and its antigenic fragments as most suitable for induction of generation of neutralizing antibodies against SARS-CoV-2 upon administration.[108]

- RBD-Dimer vaccine developed by Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences , current stage of development- Phase III (NCT04646590)
- EpiVacCorona developed by Federal Budgetary Research Institution (FBRI) State Research Center of Virology and Biotechnology "VECTOR", current stage of development- Phase III (NCT04780035).

3.2 Virus-like particle vaccines

Another type of subunit vaccines is virus-like particles (VLPs) vaccines that are composed of proteins from the viral capsid protein that do not contain infectious viral RNA or DNA. For generation of VLPs recombinant technologies, including bacterial, insect, or mammalian cell-based expression systems can also be used.[30,102] Antiviral vaccines development by this method are usually based on surface proteins that form VLPs.[109] In VLPs vaccines empty virus particles consisting multiple copies of the same antigen on their surface, by this they mimic the virus structure, leading to trigger of strong immune responses due to detection of S protein on outer surface of VLPs, and because of lack of pathogenic genetic material (DNA or RNA) VLPs vaccines have good safety profiles.[100]

4. Nucleic Acid vaccines

4.1 mRNA vaccine

mRNA vaccines consist only mRNA which encode for the antigen of interest which is specific viral structural protein and do not contain any disease-causing viral protein. Upon administration of such vaccine mRNA is taken up by host cells and translated into viral antigen resulting in stimulation of an immune response against the viral antigen. Among the CoV proteins, S protein has been the most common protein of target for mRNA vaccines.[110,112] After translation of mRNA resulting antigenic proteins triggers an immune response, and the production of antibodies.[111] mRNA vaccines are safer than inactivated or protein based vaccines because injected mRNA cannot integrate into the host's genome, also no risk of protein contamination and no risk of conversion of the injected inactivated virus to become active. As we know nature of RNA is hydrophobic with net negative charge so it can't be taken up by host cells. Hence we require a carrier molecules like lipid nanoparticle (LNPs) for mRNA vaccines intramuscular or intradermal administration of mRNA vaccines.[110,113]

- mRNA (mRNA 1273) developed by Moderna/ National Institute of Allergy and Infectious Diseases (NIAID)/ Biomedical Advanced Research and Development Authority (BARDA)/ Lonza/ Catalent/ Rovi/ Medidata/ BIOQUAL/ Baxter BioPharma Solutions/ Sanofi, current stage of development- Phase III (NCT04860297, NCT04806113, NCT04649151, NCT04470427, NCT04796896, NCT04811664, NCT04805125).
- BNT162b2 developed by BioNTech/ Pfizer/ Fosun Pharma/ Rentschler Biopharma, current stage of development- Phase III (NCT04368728, NCT04805125, NCT04800133, NCT04754594, NCT04713553, NCT04816669).

4.2 DNA vaccines

DNA vaccine consists of gene fragments of virus which are encoding for immunogenic antigens after administration into the host's cells by using DNA plasmids as a vector, they induces both humoral and cell-mediated immune responses efficiently. DNA vaccine formulation upon administration DNA plasmids vector are translocated to the host's cell nucleus, leading to activation of mammalian promoter present in the vector structure, they triggers the transcription of the gene present in the vaccine formulation to antigenic proteins through the host's cellular machinery.[113,114] Immature dendritic Cells present this antigens to the CD4+ and

CD8+ T cells in association with MHC 2 and MHC 1 antigens on the cell surface hence stimulating effective humoral as well as cell-mediated immune responses.[114,115] DNA vaccines have several advantages, over traditional live or attenuated vaccines, such as induction of broad immune responses, both cellular and humoral response, without any risk of replication of microorganisms. It is possible to construct a vector encoding different antigens of microorganisms in a single vaccine. Along with that DNA vaccines production cost is low and have high storage stability.[113]

5. Viral vector vaccine

In viral vector vaccine a safe virus/ modified virus is serve as a vector to deliver specific viral genes of interest of pathogenic virus to host cells which code for a antigenic proteins of virus and can trigger an immune response without causing disease.[116,117] Adenovirus and poxvirus are been modified to carry genes of interest usually the S gene for CoV of interest.[30,118] The advantages of viral vectors vaccines are high efficiency gene transduction, highly specific delivery of genes to target cells, induction a robust cytotoxic T lymphocyte (CTL) response to eliminate virus-infected cells. Hence have a great potential for prophylactic use.[108,119]

- Ad5-nCoV (Convidecia) developed by CanSino Biologics/ Beijing Institute of Biotechnology/ Petrovax, current stage of development- Phase III (NCT04526990, NCT04540419).
- Gam-COVID-Vac(Sputnik V) developed by Gamaleya Research Institute, current stage of development- Phase III (NCT04640233, NCT04642339, NCT04656613, NCT04564716, NCT04530396, NCT04954092).
- Ad26.COV2-S (JNJ-78436725) developed by Janssen Pharmaceutical Companies/ Beth Israel Deaconess Medical Center/ Emergent BioSolutions/ Catalent/ Biological E/ Grand River Aseptic Manufacturing (GRAM)/ Sanofi/ Merck, current stage of development- Phase III (NCT04838795, NCT04505722, NCT04614948).
- COVID-19 Vaccine AstraZeneca developed by University of Oxford, Oxford Biomedica, Vaccines Manufacturing and Innovation Centre, Pall Life Sciences, Cobra Biologics, HalixBV, Advent s.r.l., Merck KGaA, the Serum Institute, Vaccitech, Catalent, CSL, and AstraZeneca/IQVIA, current stage of development- Phase III (NCT04864561,CTRI/2020/08/027170, NCT04800133, NCT04536051, NCT04516746, NCT04400838, NCT04540393, NCT04885764)
- Covishield manufactured by Serum Institute of India. Current stage of development-Phase III (CTRI/2020/08/027170)

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